



US009273294B2

(12) **United States Patent**
Yu et al.

(10) **Patent No.:** US 9,273,294 B2
(45) **Date of Patent:** Mar. 1, 2016

(54) **TARGETED 2'-O-METHYLATION OF TELOMERASE NON-CODING RNA**

(75) Inventors: **Yi-Tao Yu**, Rochester, NY (US); **Chao Huang**, Rochester, NY (US)

(73) Assignee: **University of Rochester**, Rochester, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 189 days.

(21) Appl. No.: **13/809,975**

(22) PCT Filed: **Jul. 15, 2011**

(86) PCT No.: **PCT/US2011/044237**

§ 371 (c)(1),
(2), (4) Date: **Mar. 27, 2013**

(87) PCT Pub. No.: **WO2012/009667**

PCT Pub. Date: **Jan. 19, 2012**

(65) **Prior Publication Data**

US 2013/0196409 A1 Aug. 1, 2013

Related U.S. Application Data

(60) Provisional application No. 61/365,265, filed on Jul. 16, 2010.

(51) **Int. Cl.**

C12N 15/00 (2006.01)
C07H 21/02 (2006.01)
C12N 9/12 (2006.01)
C12N 15/11 (2006.01)

(52) **U.S. Cl.**

CPC **C12N 9/1276** (2013.01); **C12N 15/11** (2013.01); **C12Y 207/07049** (2013.01); **C12N 2310/113** (2013.01); **C12N 2310/321** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,972,705 A * 10/1999 Fournier et al. 435/440

OTHER PUBLICATIONS

Ge et al. ('Regulation of pre-mRNA splicing in Xenopus oocytes by targeted 2'-O-methylation' RNA, vol. 16(5), pp. 1078-1085 (2G Mar. 2010)).*

Allshire R.C. et al., "Human telomeres contain at least three types of G-rich repeat distributed non-randomly," *Nucleic Acids Res.* 17:4611-4627, IRL Press, United Kingdom (1989).

Bachellerie, J. P., et al., "Antisense snoRNAs: a family of nucleolar RNAs with long conriplementarities to rRNA," *Trends Biochem. Sci.* 20:261-264, Elsevier Science Ltd., England (1995).

Balakin, et al., "The RNA World of the Nucleolus: Two Major Families of Small RNAs Defined by Different Box Elements with Related Functions," *Cell* 86:823-834, Cell Press, United States (1996).

(Continued)

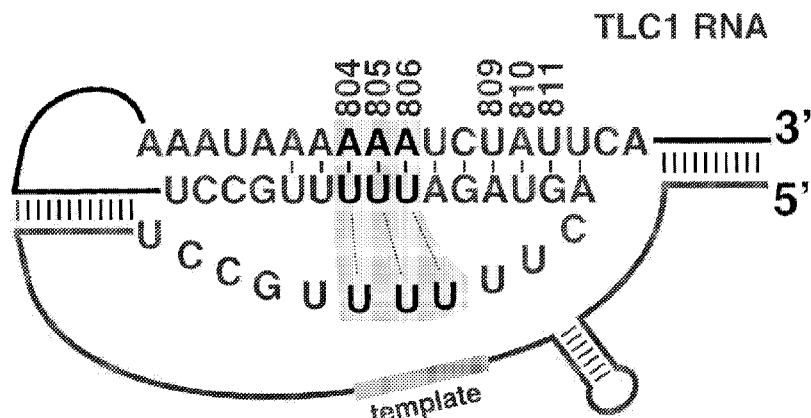
Primary Examiner — Richard Schnizer

(74) *Attorney, Agent, or Firm* — Sterne, Kessler, Goldstein & Fox P.L.L.C.

(57) **ABSTRACT**

Processes and C/D box small nucleolar RNAs (snoRNAs) for altering telomerase activity and altering telomerase length are described. The processes of the invention involve the use of C/D box snoRNAs for targeted 2'-O-methylation modification of nucleotides in a pseudoknot region of the telomerase RNA. Depending on their position, the 2'-O-methylation modifications can cause an increase in telomerase activity and subsequent telomere lengthening or a decrease in telomerase activity and subsequent telomere shortening.

4 Claims, 17 Drawing Sheets



(56)

References Cited**OTHER PUBLICATIONS**

- Bazarov, A.V., et al., "P16^{INK4a} Mediated Suppression of Telomerase in Normal and Malignant Human Breast Cells," *Aging Cell* 9(5):736-746, Wiley-Blackwell, England (2010).
- Blackburn, E. H., et al., "Telomeres and telomerase: the path from maize, *Tetrahymena* and yeast to human cancer and aging," *Nat. Med.* 12:1133-1138, Nature Publishing Company, United States (2006).
- Blasco, M. A., "Telomere length, stem cells and aging," *Nat. Chem. Biol.* 3(10):640-649, Nature Publishing Group, United States (2007).
- Cavaillé, J., M. et al., "Targeted ribose methylation of RNA in vivo directed by tailored antisense RNA guides," *Nature* 383:732-735, Macmillan Journals Ltd., England (1996).
- Cawthon, R.M., "Telomere measurement by quantitative PCR," *Nucleic Acids Res.* 30(10):e47, 6 pages, Oxford University Press, England (2002).
- Cech, T. R., "Beginning to Understand the End of the Chromosome," *Cell* 116:273-279, Cell Press, United States (2004).
- Cien, J-L. and Greider, C.W., "Functional analysis of the pseudoknot structure in human telomerase RNA," *Proc. Natl. Acad. Sci. USA* 102:8080-8085, The National Academy of Sciences, Untied States (2005).
- Chen, S.M., et al., "Effect of blocking VEGF, hTERT and Bcl-xL by multiple shRNA expression vectors on the human laryngeal squamous carcinoma xenograft in nude mice," *Cancer Biol. Ther.* 7(5):734-739, Landes Bioscience, United States (2008).
- Collins, K., "The biogenesis and regulation of telomerase holoenzymes," *Nat. Rev. Mol. Cell Biol.* 7:484-494, Nature Pub. Group, England (2006).
- Coussens, M., et al., "RNAi screen for telomerase reverse transcriptase transcriptional regulators identifies HIF α as critical for telomerase function in murine embryonic stem cells," *Proc. Natl. Acad. Sci. USA* 107(31): p. 13842-13847, The National Academy of Sciences, Untied States (2010).
- Culver, G. M., et al., "A 2'-Phosphotransferase Implicated in tRNA Splicing Is Essential in *Saccharomyces cerevisiae*," *J Biol. Chem.* 272:13203-13210, The American Society for Biochemistry and Molecular Biology, Inc., United States (1997).
- Darzacq, X., et al., "Cajal body-specific small nuclear RNAs: a novel class of 2'-O-methylation and pseudouridylation guide RNAs," *EMBO J* 21:2746-2756, European Molecular Biology Organization, Germany (2002).
- Deryusheva, S. and Gall, J.G., "Small Cajal Body-specific RNAs of *Drosophila* Function in the Absence of Cajal Bodies," *Mol. Biol. Cell* 20(24):5250-5259, The American Society for Cell Biology, United States (2009).
- Fatica, A., et al., "Yeast snoRNA accumulation relies on a cleavage-dependent/polyadenylation-independent 3'-processing apparatus," *EMBO J* 19:6218-6229, Oxford University Press, England (2000).
- Friedman, K. L., et al., "Essential functions of amino-terminal domains in the yeast telomerase catalytic subunit revealed by selection for viable mutants," *Genes Dev.* 13:2863-2874, Cold Spring Harbor Laboratory Press, United States (1999).
- Gardner, P.P., et al., "Rfam: Wikipedia, clans and the 'decimal' release," *Nucleic Acids Research* 39:D141-D145, Oxford University Press, England (2010).
- Ge, J., et al., "Regulation of pre-mRNA splicing in *Xenopus oocytes* by targeted 2'-O-methylation," *RNA* 16:1078-1085, Cold Springs Harbor Laboratory Press, United States (2010).
- Gottschling, D. E., et al., "Position Effect at *S. cerevisiae* Telomeres: Reversible Repression of Pol II Transcription," *Cell* 63:751-762, Cell Press, United States (1990).
- Greider, C. W. and Blackburn, E.H., "Identification of a Specific Telomere Terminal Transferase Activity in *Tetrahymena* Extracts," *Cell* 43:405-413, Cell Press, United States (1985).
- Hou, Y. M., et al., "An important 2'-OH group for an RNA-protein interaction," *Nucleic Acids Res.* 29:976-985, Oxford University Press, England (2001).
- Huang, C. and Yu, Y.-T., "Targeted 2'-O Methylation at a Nucleotide within the Pseudoknot of Telomerase RNA Reduces Telomerase Activity in Vivo," *Mol. Cell Biol.* 30(18):4368-4378, American Society for Microbiology, United States (2010).
- Huang, C., et al., "Post-transcriptional Modification of RNAs by Artificial Box H/ACA and Box C/D RNPs," *Methods Mol. Biol.* 718:227-244, Springer Science, United States (2011).
- Kim, N.W., et al., "Specific association of Human Telomerase Activity with Immortal Cells and Cancer," *Science* 266:2011-2015, American Association for the Advancement of Science, United States (1994).
- Kiss-Laszlo, Z., et al., "Site-Specific Ribose Methylation of Preribosomal RNA: A Novel Function for Small Nucleolar RNAs," *Cell* 85:1077-1088, Cell Press, United States (1996).
- Kiss, T., "Small nucleolar RNA-guided post-transcriptional modification of cellular RNAs," *EMBO J* 20:3617-3622, European Molecular Biology Organization, Germany (2001).
- Kiss, T., et al., "Small Nucleolar RNAs: An Abundant Group of Noncoding RNAs with Diverse Cellular Functions," *Cell* 109:145-148, Cell Press, United States (2001).
- Kosciolek, B.A., et al., "Inhibition of Telomerase Activity in Human Cancer Cells by RNA Interference," *Mol. Cancer Ther.* 2(3):209-216, American Association for Cancer Research, United States (2003).
- Lestrade, L., and Weber, M. J. "snoRNA-LBME-db, a comprehensive database of human H/ACA and C/D box snoRNAs," *Nucleic Acids Res.* 34(database issue): D158-162, Oxford University Press, England (2006).
- Li, S., et al., "Rapid Inhibition of Cancer Cell Growth Induced by Lentiviral Delivery and Expression of Mutant-Template Telomerase RNA and Anti-telomerase Short-Interfering RNA," *Cancer Res.* 64(14):4833-4840, American Association for Cancer, United States (2004).
- Hang, X. H., et al., "The spliced leader-associated RNA is a trypanosome-specific sn(o) RNA that has the potential to guide pseudouridine formation on the SL RNA," *RNA* 8:237-246, Cambridge University Press, United States (2002).
- Lingner, J., et al., "Reverse Transcriptase Motifs in the Catalytic Subunit of Telomerase," *Science* 276:561-567, American Association for the Advancement of Science, United States (1997).
- Liu, B., et al., "Probing RNA in Vivo with Methylation Guide Small Nucleolar RNAs," *Methods* 23(3):276-286, Academic Press, United States (2001).
- Ma, X., et al., "Pseudouridylation of yeast U2 snRNA is catalyzed by either an RNA-guided or RNA-independent mechanism," *EMBO J* 24:2403-2413, European Molecular (2005).
- Maden, B. E. H., et al., "Classical and novel approaches to the detection and localization of the numerous modified nucleotides in eukaryotic ribosomal RNA," *Biochimie* 77:22-29, Elsevier, France (1995).
- Maurelli, R., et al., "Inactivation of p16INK4a (inhibitor of cyclin-dependent kinase 4A) immortalizes primary human keratinocytes by maintaining cells in the stem cell compartment," *FASEB J* 20(9):1516-1518, The Federation, United States (2006).
- Miller, M. C. and Collins, K., "Telomerase recognizes its template by using an adjacent RNA motif," *Proc. Natl. Acad. Sci. USA* 99:6585-6590, The National Academy of Sciences, United States (2002).
- Patry, C., et al., "Small Interfering RNA-Mediated Reduction in Heterogeneous Nuclear Ribonucleoparticule A1/A2 Proteins Induces Apoptosis in Human Cancer Cells but not in Normal Mortal Lines," *Cancer Res* 63(22):7679-7688, American Association for Cancer Research, United States (2003).
- Peculis, B., "RNA processing: Pocket guides to ribosomal RNA," *Curr. Biol.* 7:R480-R482, Elsevier Inc., United States (1997).
- Podlevsky, J.D., et al., "The Telomerase Database," *Nucleic Acids Res.* 36(database issue):D339-D343, Oxford University Press, England (2008).
- Qiao, F., et al., "Triple-helix structure in telomerase RNA contributes to catalysis," *Nat. Struct. Mol. Biol.* 15:634-640, Nature Publishing Group, United States (2008).
- Rufer, N. et al., "Telomere length dynamics in human lymphocyte subpopulations measured by flow cytometry," *Nat. Biotechnol.* 16: 743-747, Nature Publishing Group, United States (1998).

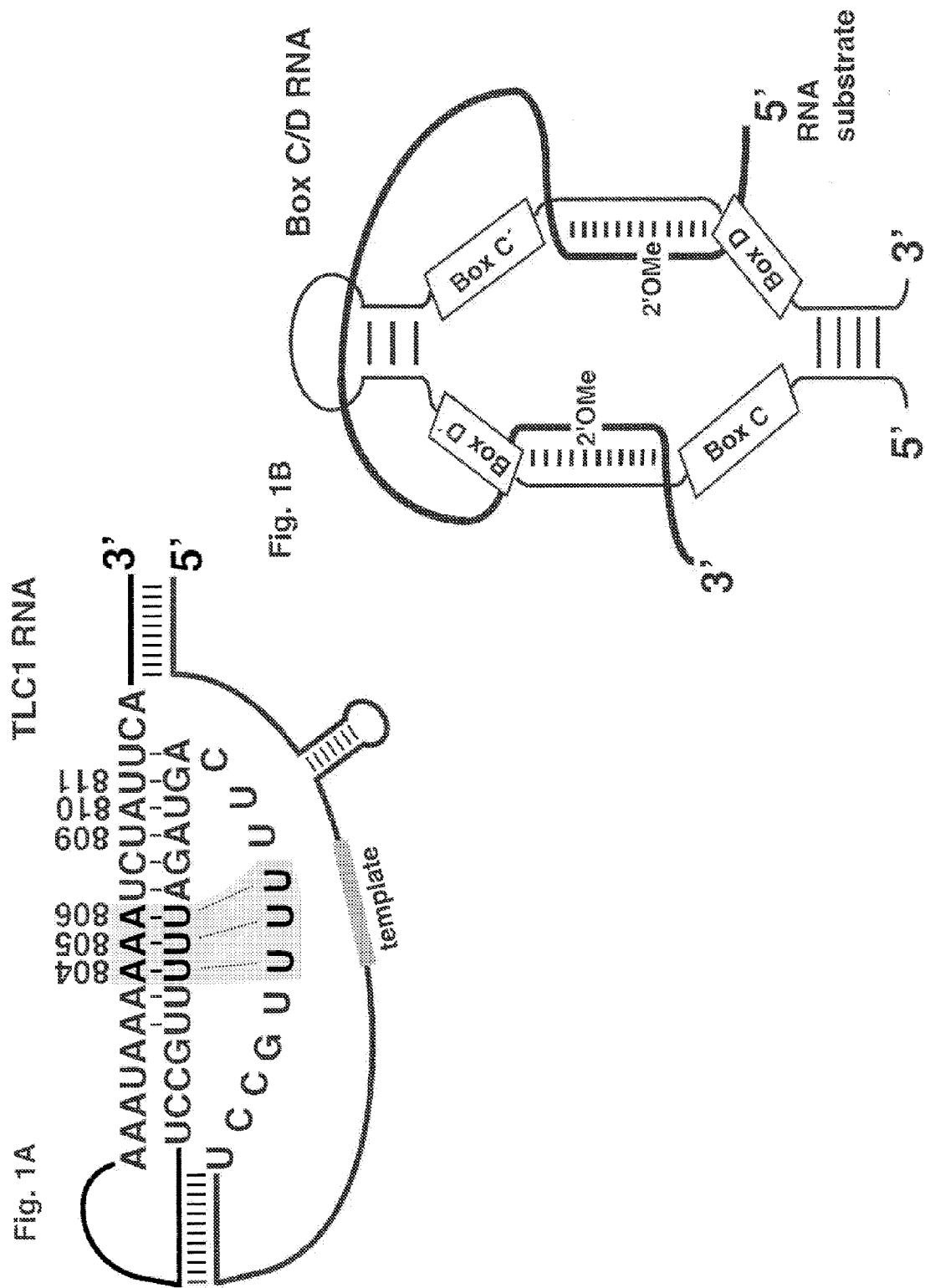
(56)

References Cited

OTHER PUBLICATIONS

- Saikia, M., et al., "A systematic, ligation-based approach to study RNA modifications," *RNA* 12:2025-2033, Cold Spring Harbor Laboratory Press, United States (2006).
- Seto, A. G., et al., "A template-proximal RNA paired element contributes to *Saccharomyces cerevisiae* telomerase activity," *RNA* 9:1323-1332, Cold Spring Harbor Laboratory Press, United States (2003).
- Seto, A. G., et al., "Saccharomyces cerevisiae telomerase in an Sm small nuclear ribonucleoprotein particle," *Nature* 101:177-180, Macmillan Magazines Ltd., England (1999).
- Shefer, K., et al., "A Triple Helix within a Pseudoknot Is a Conserved and Essential Element of Telomerase RNA," *Mol. Cell Biol.* 27:2130-2143, American Society for Microbiology, United States (2007).
- Sijen, T., et al., "On the Role of RNA Amplification in dsRNA-Triggered Gene Silencing," *Cell* 107(4):465-476, Cell Press, United States (2001).
- Singer, M. S. and Gottschling, D.E., "TLC1: Template RNA Component of *Saccharomyces cerevisiae* Telomerase," *Science* 266:404-409, American Association for the Advancement of Science, United States (1994).
- Smith, C. M. and Steitz, J.A., "Sno Storm in the Nucleolus: New Roles for Myriad Small RNPs," *Cell* 89:669-672, Cell Press, United States (1997).
- Szostak, J. W. and Blackburn, E. H., "Cloning Yeast Telomeres on Linear Plasmid Vectors," *Cell* 29:245-255, Cell Press, United States (1982).
- Theimer, C. A., et al., "Structure of the Human Telomerase RNA Pseudoknot Reveals Conserved Tertiary Interactions Essential for Function," *Mol. Cell* 17:671-682, Elsevier Inc., United States (2005).
- Tycowski, K.T., et al., "A mammalian gene with introns instead of exons generating stable RNA products," *Nature* 379(6564):464-466, Nature Publishing Group, United States (1996).
- Uesugi, S., et al., "A Linear Relationship Between Electronegativity of 2'-Substituents and Conformation of Adenine Nucleosides," *Tetrahedron Letters* 20:4073-4076, Pergamon Press Ltd., England (1979).
- Wang, Y., et al., "Application of combination of short hairpin RNA segments for silencing *VEGF*, *TERT*, and *Bcl-xL* expression in laryngeal squamous carcinoma," *Cancer Biol. Ther.* 7(6):896-901, Landes Bioscience United States (2008).
- Yu, Y. T., et al., "Mechanisms and functions of RNA-guided RNA modification," in *Fine-Tuning of RNA functions by Modification and Editing*, vol. 12, H. Grosjean (Ed.), 40 pages, Springer-Verlag, Germany (2005).
- Yu, Q., et al., "Saccharomyces cerevisiae Linker Histone H10p Functionally Interacts with Core Histone H4 and Negatively Regulates the Establishment of Transcriptionally Silent Chromatin*~," *J Biol. Chem.* 284:740-750, The American Society for Biochemistry and Molecular Biology, United States (2009).
- Zappulla, D. C., et al., "Yeast telomerase RNA: A flexible scaffold for protein subunits," *Proc. Natl. Acad. Sci. USA* 101:10024-10029, The National Academy of Sciences, United States (2004).
- Zhao, X. and Yu, Y-T., "Targeted pre-mRNA modification for gene silencing and regulation," *Nat. Methods* 5(1):95-100, Nature Publishing Group, United States (2008).
- Zhao, X., et al., "An H/ACA guide RNA directs U2 pseudouridylation at two different sites in the branchpoint recognition region in *Xenopus oocytes*," *RNA* 8:1515-1525, Cambridge University Press, United States (2002).
- Zhao, X., et al., "Pseudouridines in and near the branch site recognition region of U2 snRNA are required for snRNP biogenesis and pre-mRNA splicing in *Xenopus oocytes*," *RNA* 10:681-690, Cold Spring Harbor Laboratory Press, United States (2004).

* cited by examiner



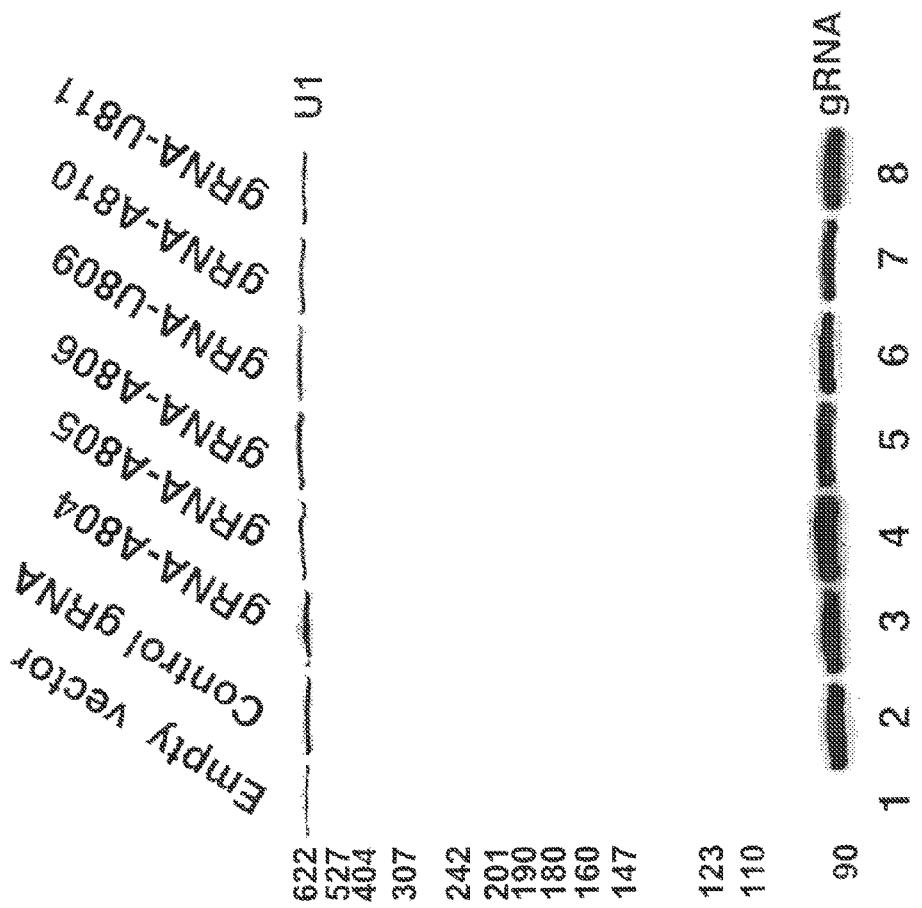
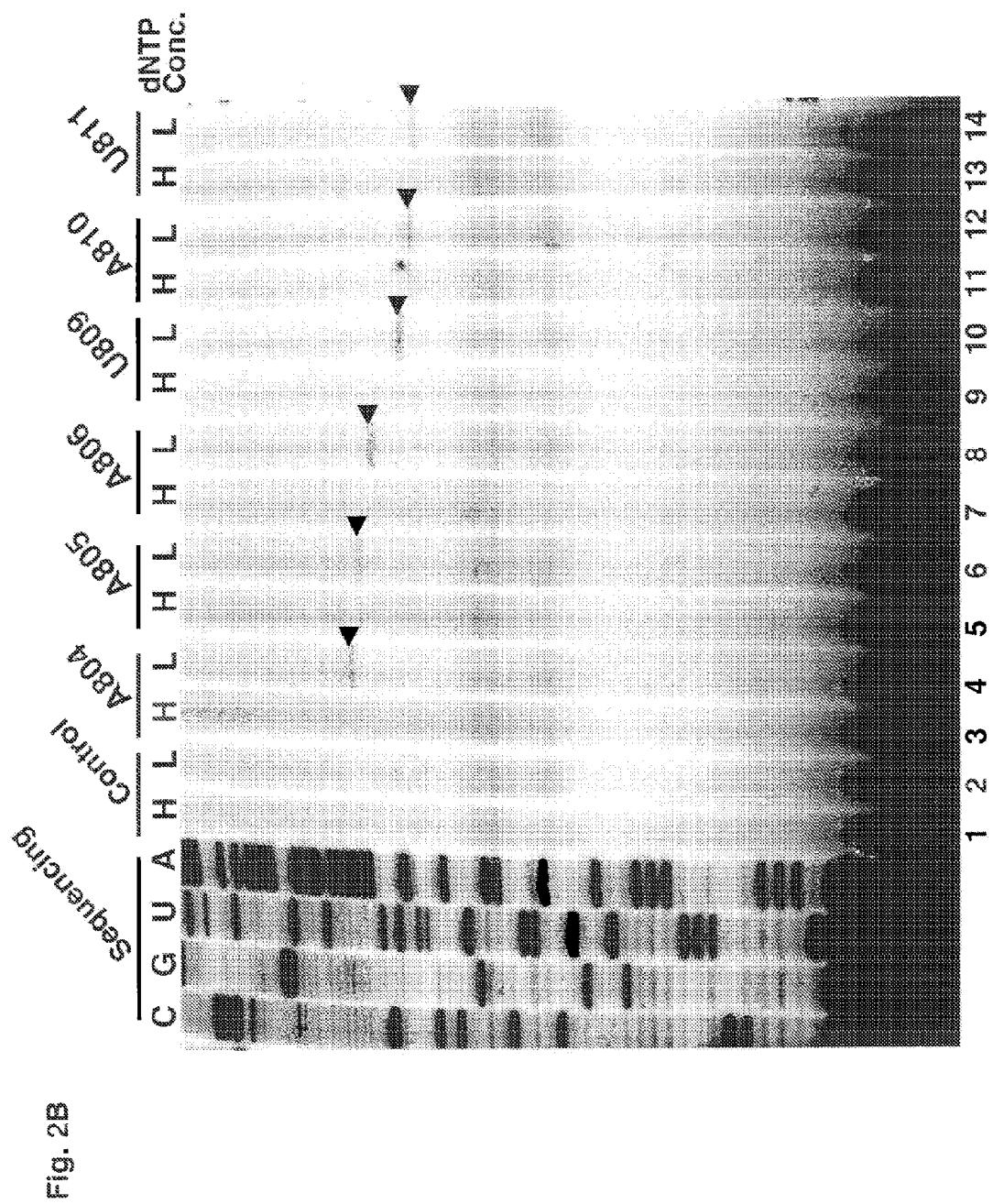


Fig. 2A



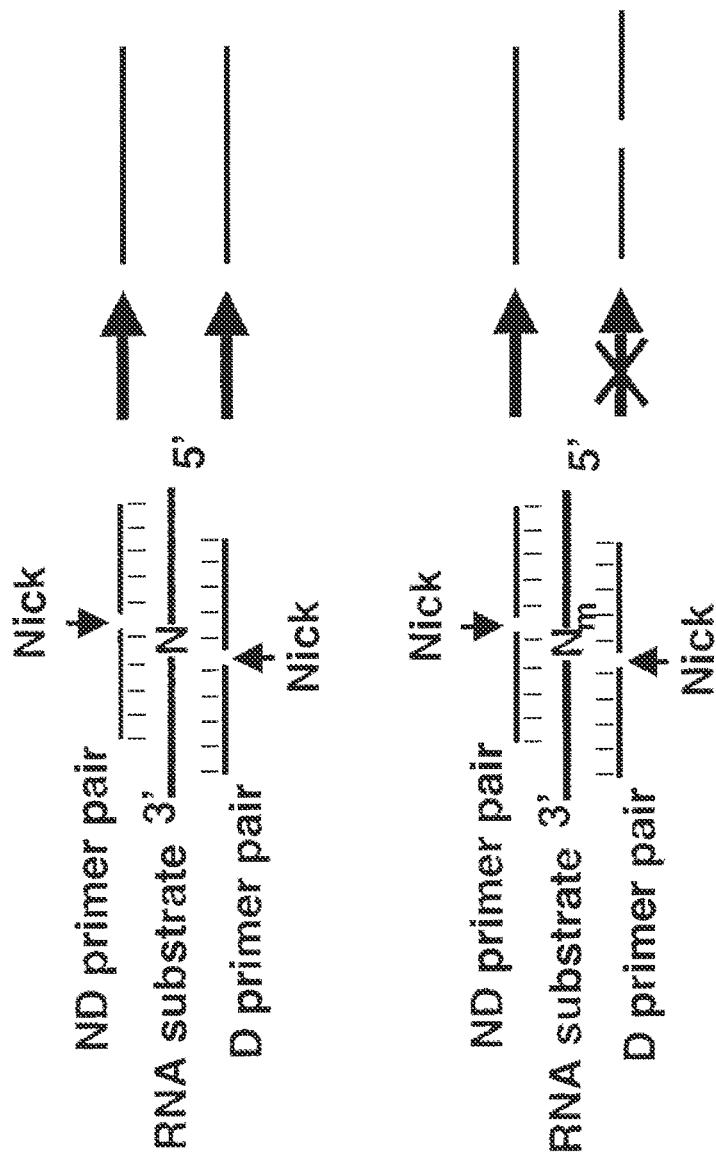


Fig. 2C

Fig. 2D

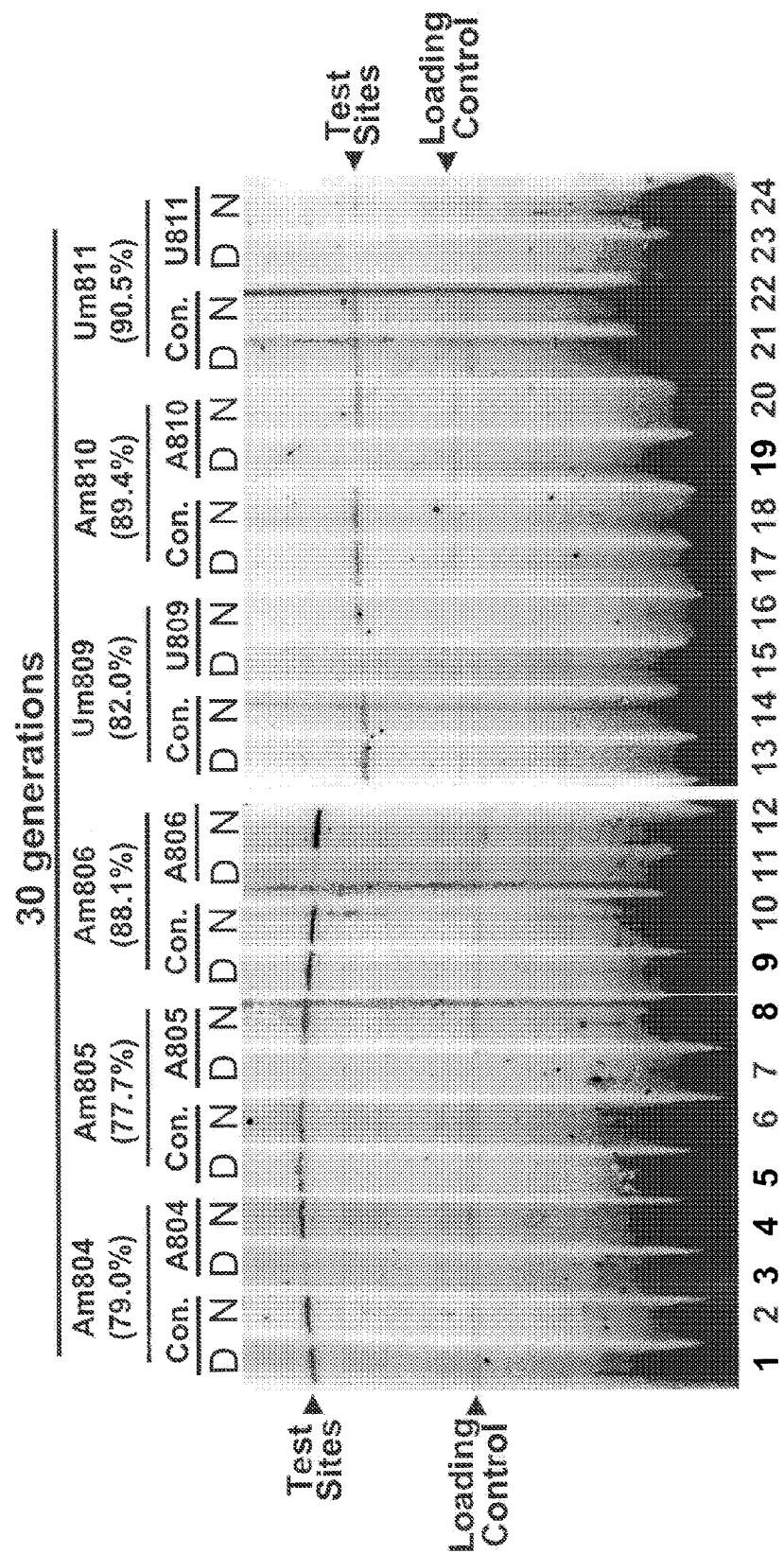
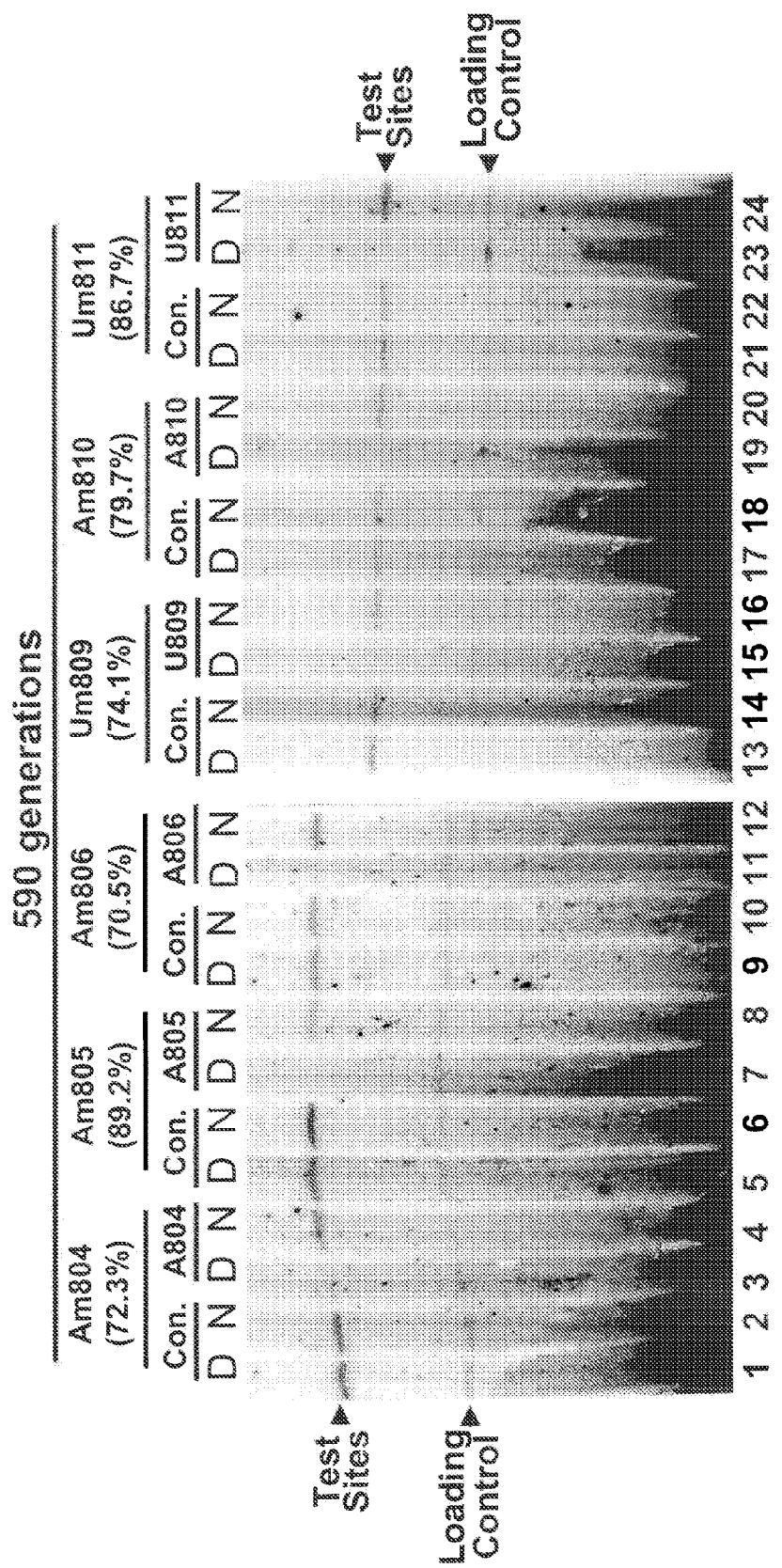


Fig. 2E



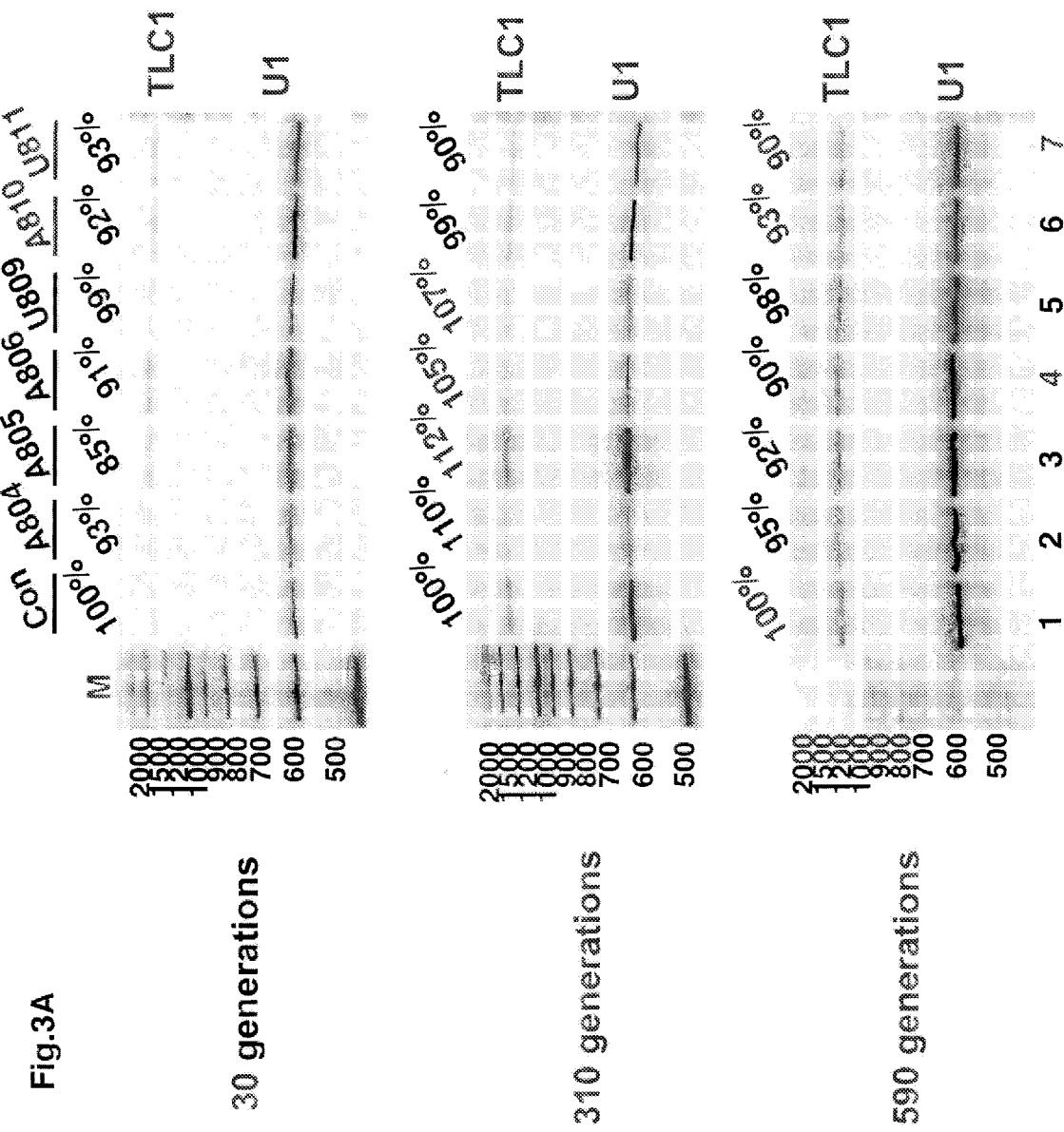
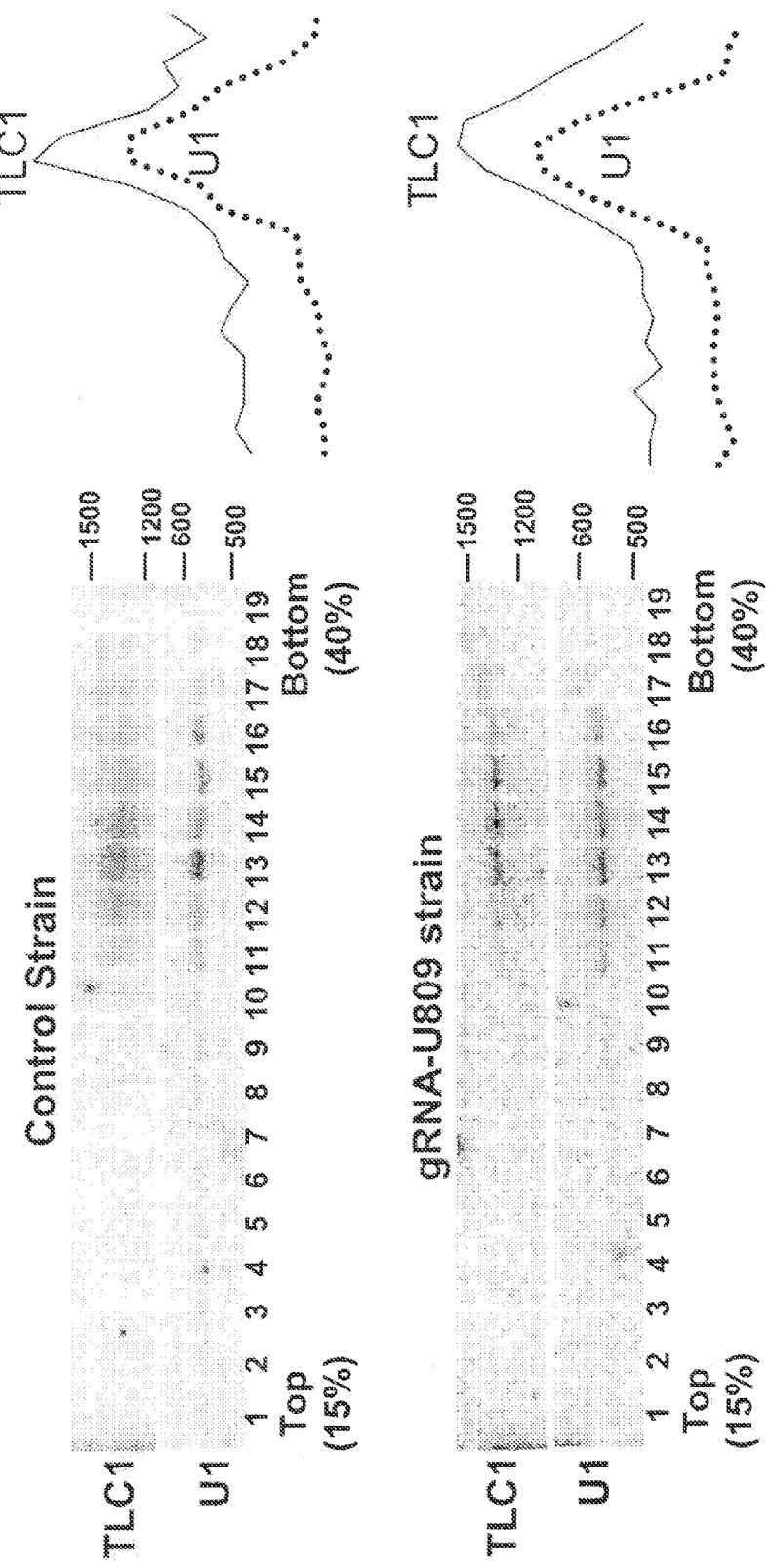


Fig. 3B



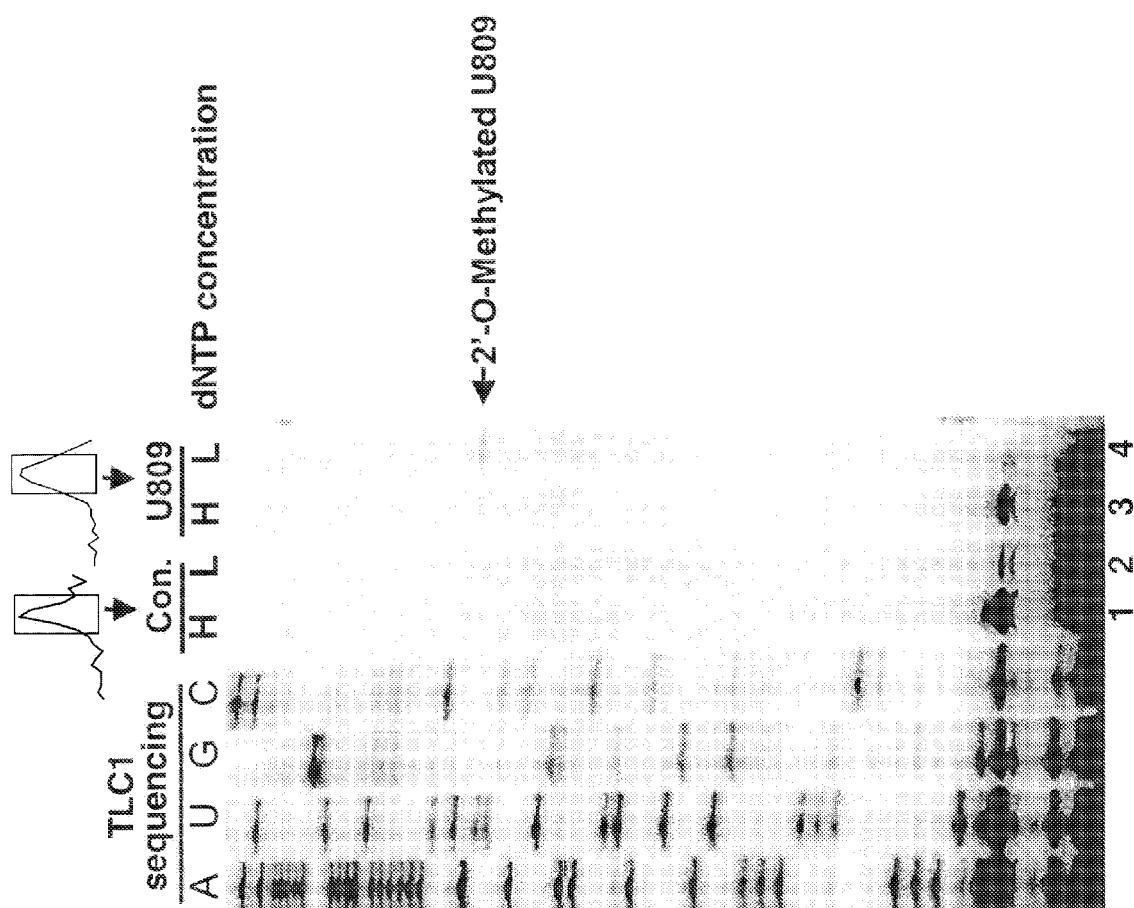


Fig. 3C

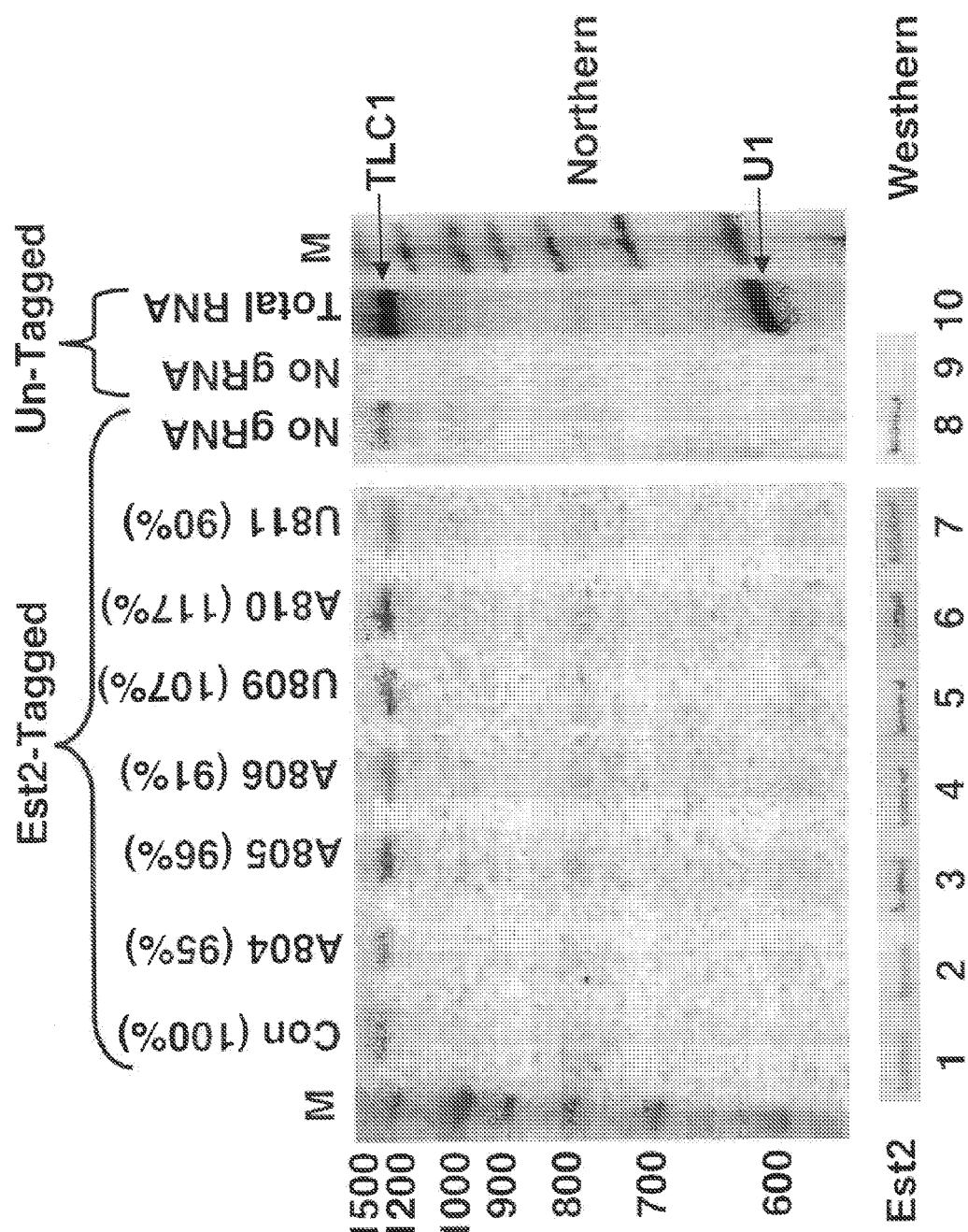


Fig. 3D

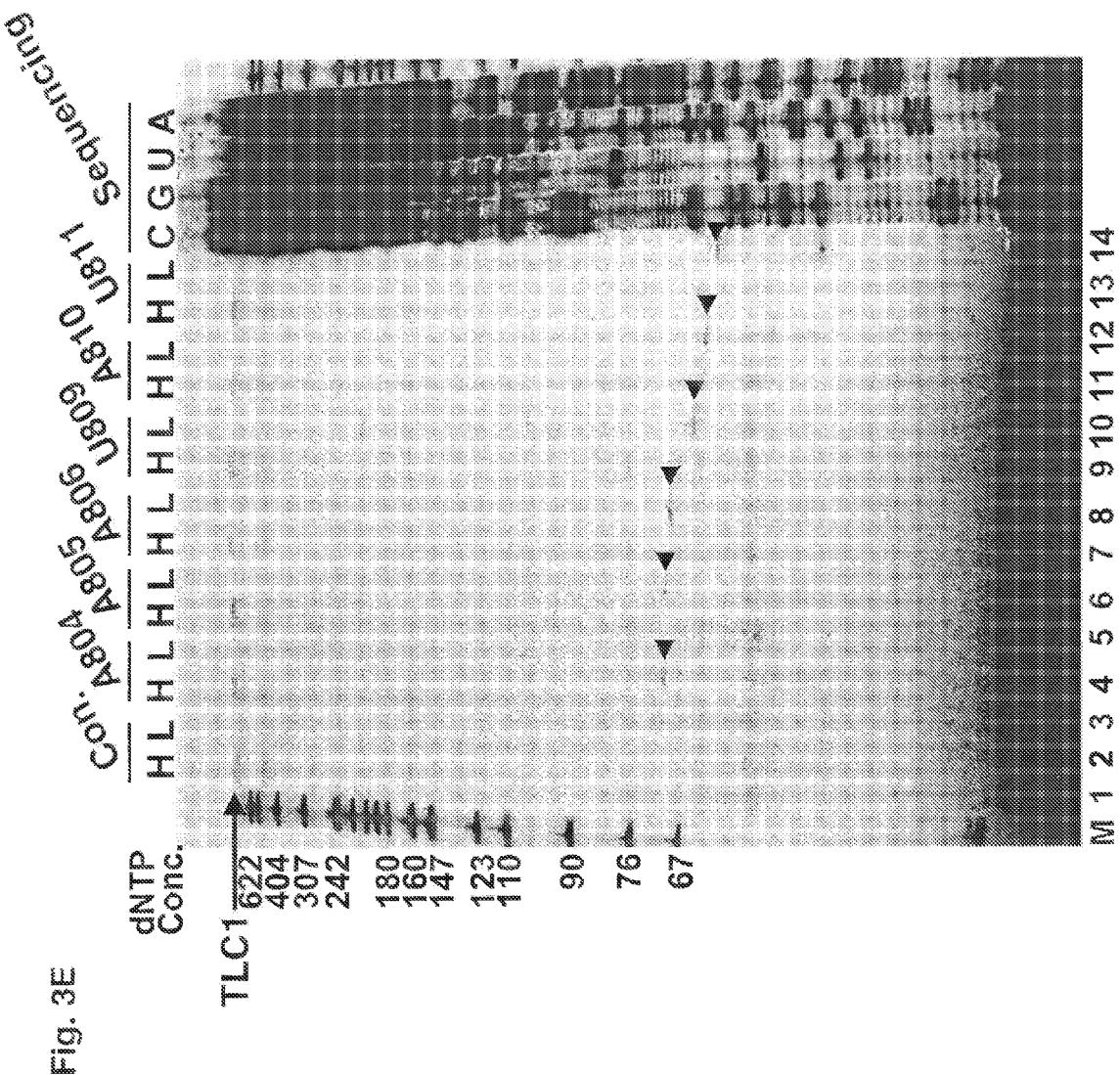
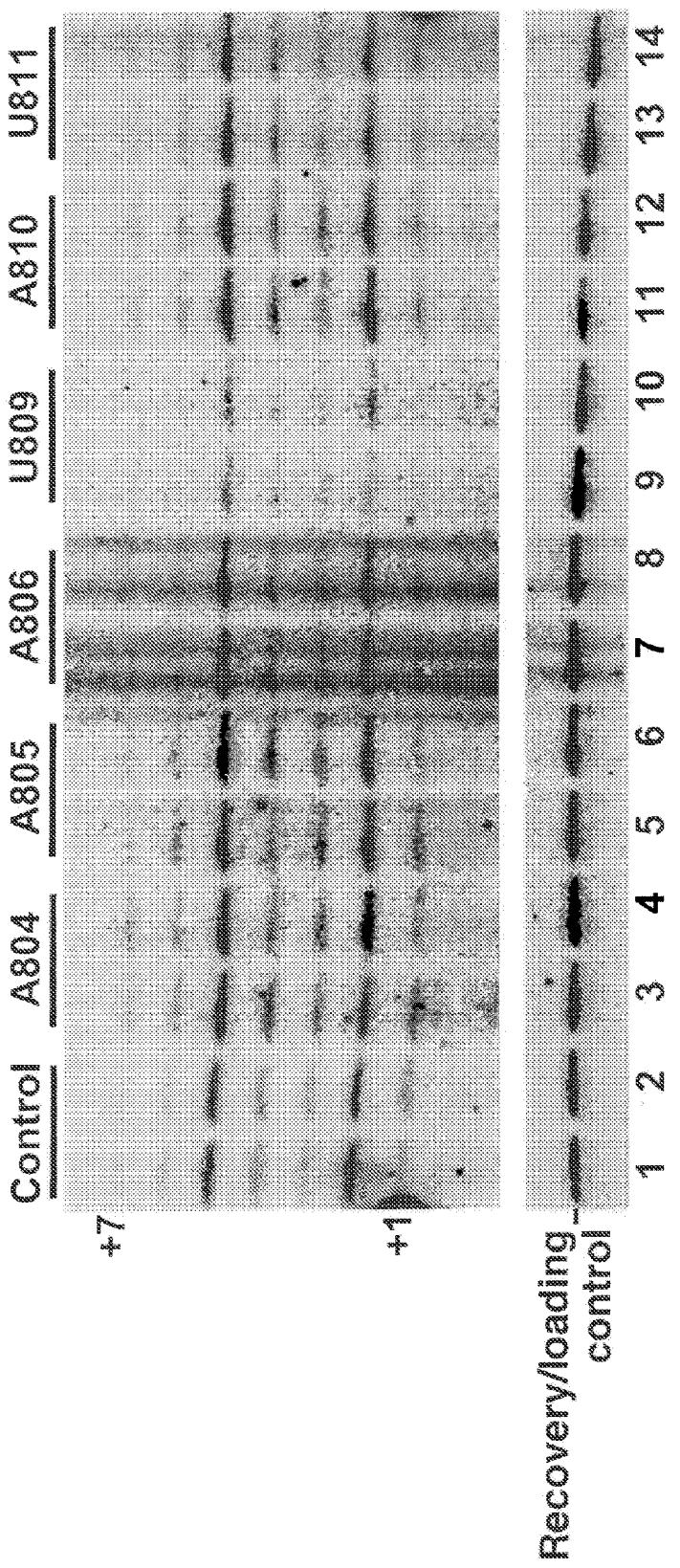


Fig 4A



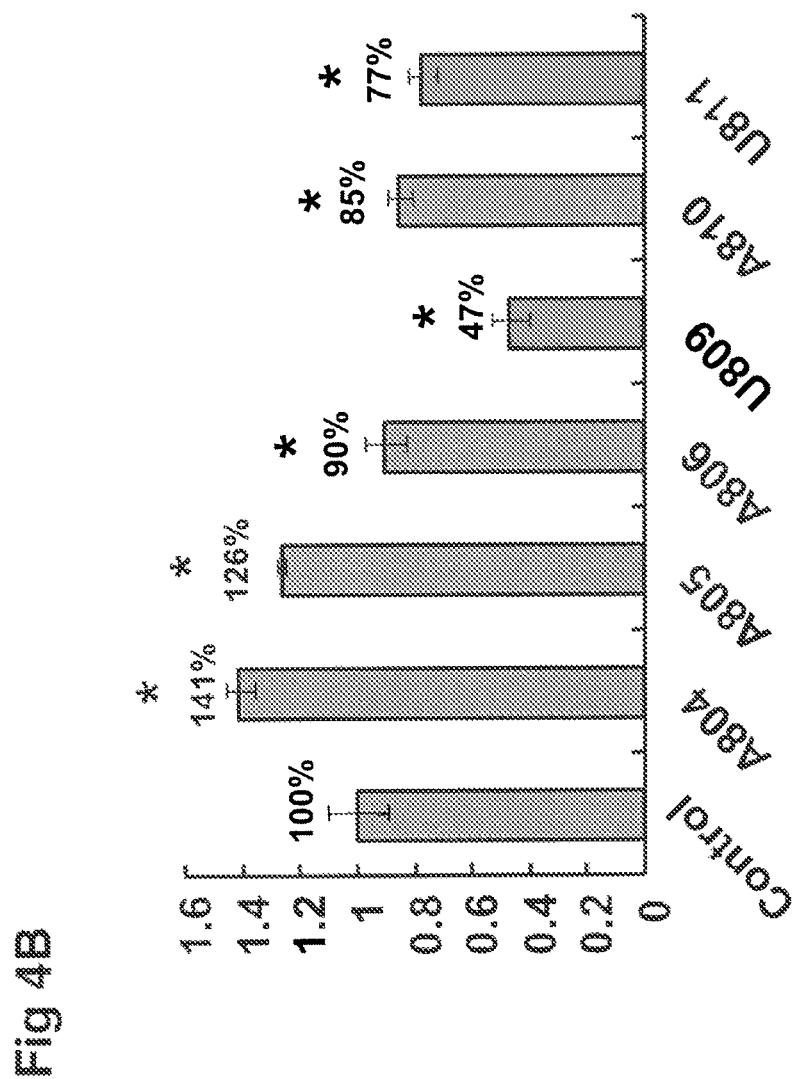


Fig. 5

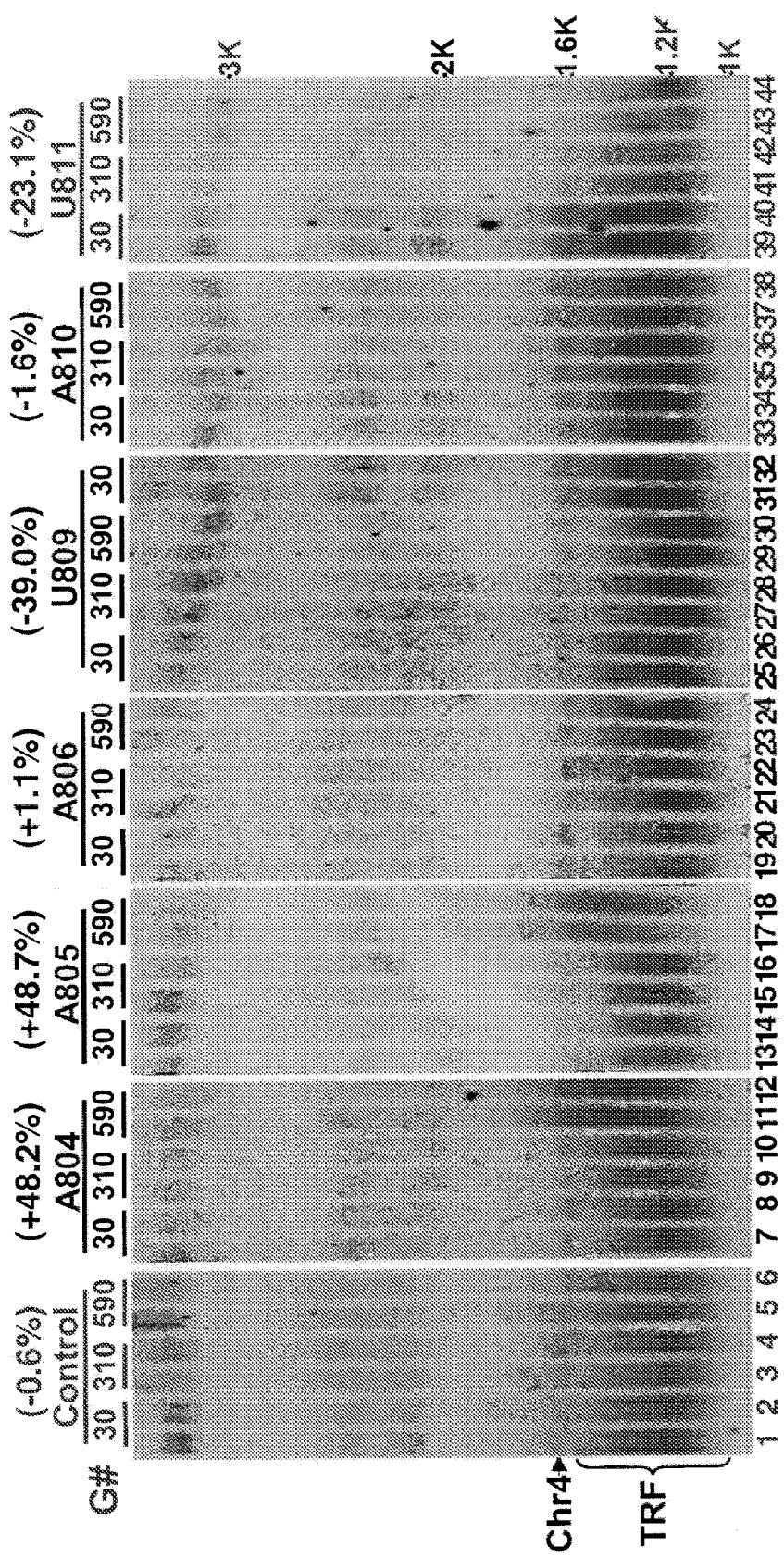
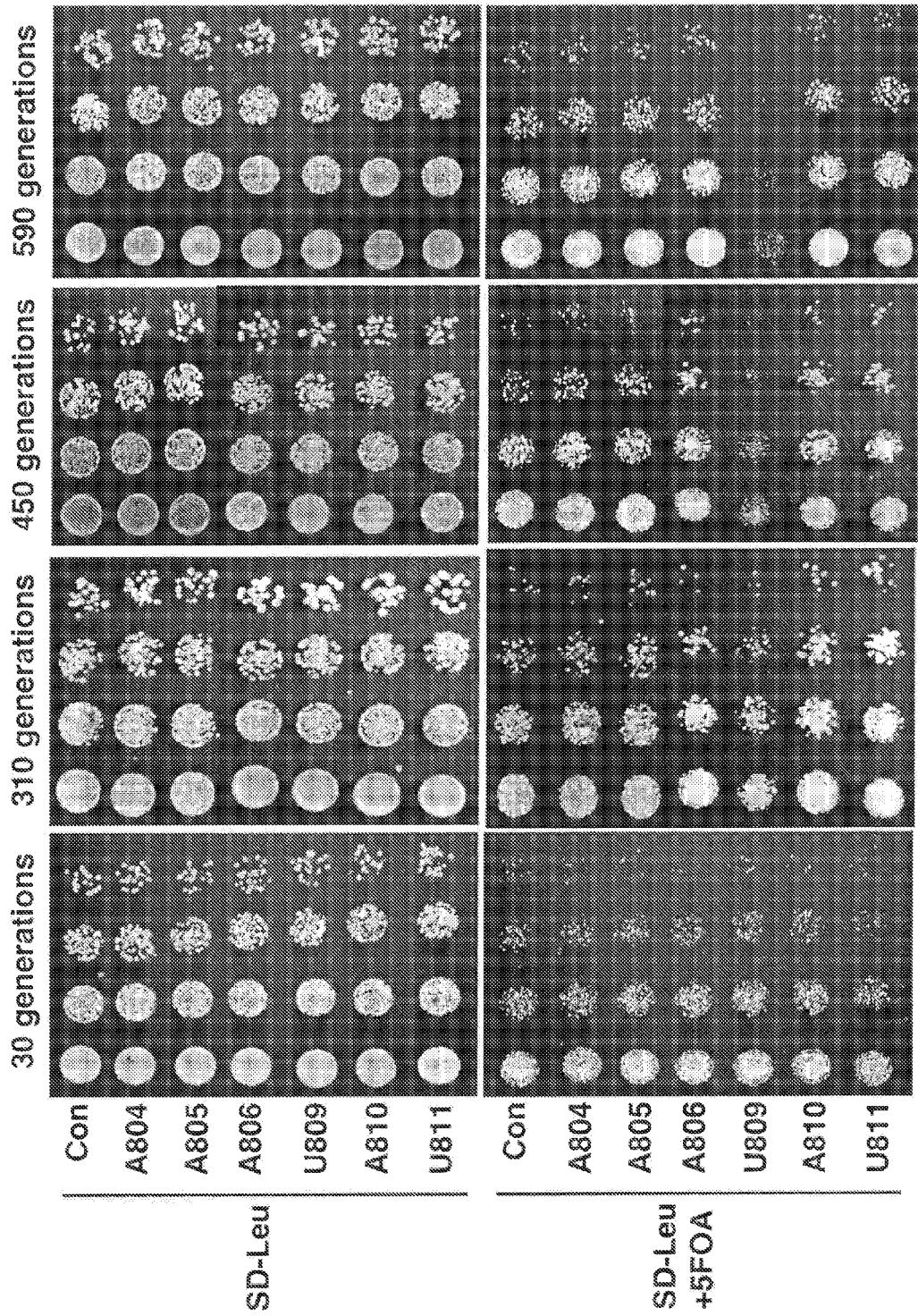


Fig. 6A



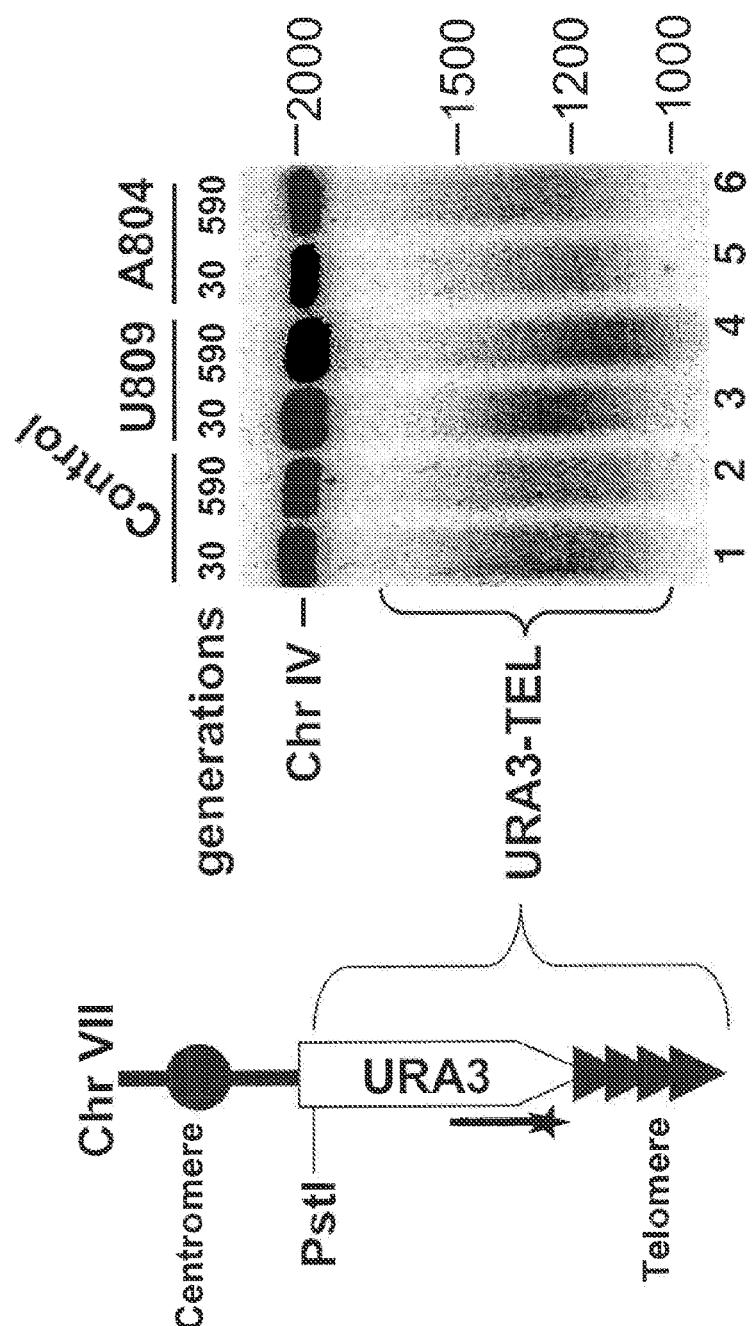


Fig. 6B

Fig. 7

1

**TARGETED 2'-O-METHYLATION OF
TELOMERASE NON-CODING RNA**

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with U.S. Government support under grant number GM62937, awarded by the National Institutes of Health. The U.S. Government has certain rights in this invention.

**REFERENCE TO SEQUENCE LISTING
SUBMITTED ELECTRONICALLY**

The content of the electronically submitted sequence listing (Name: 2973.0010001_SeqListing_Updated; Size: 125, 052 bytes; and Date of Creation: May 20, 2015) filed with the application is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention relates generally to methods for causing a 2'-O-methylation modification of a nucleotide in the telomerase RNA by contacting the telomerase RNA with a C/D snoRNA engineered to guide the 2'-O-methylation modification. The invention further relates generally to methods for modulating telomerase activity through 2'-O-methylation modification of a nucleotide in the telomerase RNA by contacting the telomerase RNA component with a C/D snoRNA engineered to guide the 2'-O-methylation modification. The invention further relates to engineered C/D box snoRNA molecules that may direct such modifications.

BACKGROUND OF THE INVENTION

In eukaryotic cells, chromosomal ends are capped by telomeres, which are long tandem-repeat sequences complexed with proteins (Blackburn, E. H., et al., *Nat. Med.* 12:1133-8 (2006); Szostak, J. W., et al., *Cell* 29:245-55 (1982)). Telomeres maintain the integrity and stability of chromosomes, which would otherwise undergo incomplete replication, fusion or degradation with each cell division (Cech, T. R., *Cell* 116:273-9 (2004); Collins, K., *Nat. Rev. Mol. Cell. Biol.* 7:484-94 (2006)). Telomerase is responsible for telomere elongation and maintenance of chromosomal ends in most eukaryotes (Blackburn, E. H., et al., *Nat. Med.* 12:1133-8 (2006); Greider, C. W., et al., *Cell* 43:405-13 (1985)). It has long been known that telomerase is fundamental to cell survival, growth and death (Blasco, M. A., *Nat. Chem. Biol.* 3:640-9 (2007)). Telomere shortening is associated with ageing and telomerase malfunction is often associated with disease. For instance, most cancer cells have an unusually high level of telomerase activity (Kim, N. W., et al., *Science* 266:2011-5 (1994)). On the other hand, mutations in telomerase components have been linked to several degenerative diseases such as dyskeratosis congenita and aplastic anemia (Blasco, M. A., *Nat. Chem. Biol.* 3:640-9 (2007)). Thus, to understand the molecular mechanisms of these diseases and to identify new treatments, it is desirable to regulate telomerase activity *in vivo*.

Telomerase is a ribonucleoprotein (RNP) complex (Greider, C. W., et al., *Nature* 337:331-7 (1989)) that consists of one noncoding RNA (known as TERC or TR in humans and TLC1 in *Saccharomyces cerevisiae*) (Singer, M. S., et al., *Science* 266:404-9 (1994)) and several proteins, including a reverse transcriptase (TERT in humans and Est2p in *Saccharomyces cerevisiae*) (Lingner, J., et al., *Science* 276:561-7 (1997)). The telomerase non-coding RNA not only folds into

2

a structure that tethers proteins but also serves as a template for reverse transcription (Zappulla, D. C., et al., *Proc. Natl. Acad. Sci. USA* 101:10024-9 (2004)), which leads to the addition of a specific repeated sequence to the chromosome ends. *S. cerevisiae* TLC1 and its homologs in other organisms (including mammals) have been extensively studied. Several other possible functions (including catalysis) of telomerase RNA have been proposed (Miller, M. C., et al., *Proc. Natl. Acad. Sci. USA* 99:6585-90 (2002); Qiao, F., et al., *Nat. Struct. Mol. Biol.* 15:634-40 (2008)). Furthermore, NMR studies and computational modeling coupled with functional analysis have revealed a conserved triple-helix structure within the pseudoknot region of human and *K. lactis* telomerase RNAs (Shefer, K., et al., *Mol. Cell. Biol.* 27:2130-43 (2007); Theimer, C. A., et al., *Mol. Cell.* 17:671-82 (2005)). Recently, Qiao, et al. has presented experimental evidence for the presence of a similar triple-helix structure in yeast TLC1 RNA (Qiao, F., et al., *Nat. Struct. Mol. Biol.* 15:634-40 (2008))(FIG. 1A). Changes of 2'-OH groups of nucleotides in 10 and adjacent to the triple-helix region to 2'-H or 2'-OMe (2'-O-methylated) lead to reduction of telomerase activity in yeast and mammalian *in vitro* systems (Qiao, F., et al., *Nat. Struct. Mol. Biol.* 15:634-40 (2008)).

Box C/D ribonucleoproteins (RNPs) are modifying enzymes that introduce 2'-O-methylation into rRNAs and snRNAs at specific sites (Yu, Y. T., et al., in H. Grosjean (Ed.): *Fine-Tuning of RNA Functions by Modification and Editing*, vol. 12, Springer-Verlag, Berlin Heidelberg (2005)). Box C/D RNPs comprise one small RNA (box C/D RNA) and four core 25 proteins (Fibrillarin or Nop1p in *S. cerevisiae*, 15.5-kDa protein, Nop56 and Nop58) (Yu, Y. T., et al., in H. Grosjean (Ed.): *Fine-Tuning of RNA Functions by Modification and Editing*, vol. 12, Springer-Verlag, Berlin Heidelberg (2005)). A typical box C/D RNA folds into a unique secondary structure, leaving two short sequences—one between box C and box D' and one between box C' and box D—unpaired or single stranded (FIG. 1B). These single-stranded sequences function as guides that base-pair with the natural rRNA and snRNA substrates, thereby directing 2'-O-methylation at specific sites 30 (Bachellerie, J. P., et al., *Trends Biochem. Sci.* 20:261-4 (1995); Cavaille, J., M. et al., *Nature* 383:732-5 (1996); Kiss-Laszlo, Z., et al., *Cell* 85:1077-88 (1996)). Without exception, 2'-O-methylation occurs at the target nucleotide in the substrate RNA that is base-paired to the nucleotide in 35 snoRNA precisely 5 nucleotides upstream from box D (or D'; FIG. 1B) (Cavaille, J., M. et al., *Nature* 383:732-5 (1996); Kiss-Laszlo, Z., et al., *Cell* 85:1077-88 (1996)). Once the box C/D snoRNA finds its nucleotide target, fibrillarin, a methyl transferase associated with the box C/D guide RNA, delivers the methyl group to the target nucleotide at the 2'-O position. The “Box D+5 rule” for predicting the site of 2'-O-methylation guided by box C/D RNAs has been verified in various 40 organisms including yeast, *Xenopus* and human, suggesting that RNA-guided 2'-O-methylation of rRNA and snRNA is universal among eukaryotes (Kiss, T. et al., *Embo J* 20:3617-22 (2001); Kiss, T., et al., *Cell* 109:145-8 (2001); Peculis, B., *Curr. Biol.* 7:R480-2 (1997); Smith, C. M., et al., *Cell* 89:669-72 (1997)). Given the detailed mechanism of RNA-guided 45 RNA 2'-O-methylation, it is possible to design artificial box C/D RNAs to target telomerase RNA in and adjacent to the triple-helix region, thus offering an opportunity to manipulate 50 telomerase activity *in vivo*.

As disclosed in detail herein, the present inventors show that artificial box C/D RNAs can target 2'-O-methylation at specific sites in and adjacent to the triple-helix structure of 55 telomerase, thereby affecting telomerase activity *in vivo*. 2'-O-methylation did not affect the steady-state level of

TLC1, and 2'-O-methylated TLC1 was incorporated into telomerase RNP. Thus, these results indicate that telomerase activity can be manipulated in vivo.

SUMMARY OF THE INVENTION

The invention is directed to method for causing the 2'-O-methylation of a nucleotide at a specific position of a telomerase RNA by contacting the telomerase RNA with a C/D box snoRNA that causes 2'-O-methylation at the specific position in the telomerase RNA. The method may be performed in vivo. In certain embodiments, the method of the invention further entails assembling the modified telomerase RNA into a telomerase ribonucleoprotein complex.

In certain embodiments, the telomerase RNA is human telomerase RNA encoded by a nucleic acid comprising SEQ ID NO: 266. In certain embodiments, the C/D box snoRNA is encoded by a nucleic acid comprising a sequence selected from: SEQ ID NOs:300-314.

The invention is also directed to a method for altering telomerase enzymatic activity by providing a telomerase RNA and contacting the telomerase RNA component with a C/D box snoRNA that causes a 2'-O-methylation modification of a nucleotide in the telomerase RNA. In certain embodiments, the nucleotide that is 2'-O-methylated is located in the pseudoknot region of the telomerase RNA. The 2'-O-methylation modification of a nucleotide in the telomerase RNA alters the telomerase enzymatic activity, e.g., the modification may either increase or decrease telomerase activity.

The invention is also directed to a method for altering telomere length comprising providing a cell expressing telomerase with a telomerase RNA having and providing a nucleic acid encoding a C/D box snoRNA that causes a 2'-O-methylation modification of a nucleotide in the telomerase RNA in a manner that cause the guide RNA to be expressed in the cell. In certain embodiments, the nucleotide that is 2'-O-methylated is located in the pseudoknot region of the telomerase RNA. The 2'-O-methylation modification of a nucleotide in the telomerase RNA alters the length of telomeres in the cell, e.g., the modification may either increase or decrease telomere length.

The present invention is also directed to engineered C/D box snoRNA molecules that allow for targeted modification of the telomerase RNA. In certain embodiments, the invention is directed to nucleic acids encoding an engineered C/D box snoRNA, wherein the nucleic acid encodes a sequence comprising nucleic acids selected from SEQ ID NOs:300-314.

DESCRIPTION OF THE FIGURES

FIG. 1 shows schematic diagrams of the yeast telomerase RNA and a yeast Box C/D RNA. (A) The pseudoknot structure of *S. cerevisiae* TLC1 RNA is shown schematically (modified from (Qiao, F., et al., *Nat. Struct. Mol. Biol.* 15:634-40 (2008))). Shaded nucleotides and dotted lines denote the triple helix. The template sequence is also indicated. Nucleotides in the triple-helix region that were evaluated in the current work are numbered. (B) The box C/D RNA structure is shown schematically. Boxes C, D', C' and D are indicated. The sequence between box C and box D' and the sequence between box C' and box D function as guides that base-pair with target RNA (thick line), as shown. 2'OMe denotes the target nucleotide to be 2'-O-methylated. The two nucleotide sequences shown in FIG. 1A represent nucleotides 751-765 and 797-814 of SEQ ID NO: 282.

FIG. 2 shows experimental results demonstrating that Artificial box C/D guide RNAs are expressed and functional. (A) Northern blot assay for gRNA expression. Total RNA isolated from cells (yCH-001) expressing no gRNA (empty vector) (lane 1), a random (control) gRNA (lanes 2), gRNA-A804 (lane 3), gRNA-A805 (lane 4), gRNA-A806 (lane 5), gRNA-U809 (lane 6), gRNA-A810 (lane 7), or gRNA-U811 (lane 8) was used for Northern blot analysis. Probes for U1 (loading control) and gRNAs were used, and signals corresponding to these RNAs are indicated. The levels of some gRNAs are slightly lower than the others, but they were all estimated (based on northern blotting) to be higher than the endogenous naturally-occurring box C/D RNAs tested (data not shown). (B) 2'-O-methylation mapping of individually modified nucleotides. Total RNA isolated from cells (yCH-002) expressing a random gRNA (control; lanes 1 and 2), gRNA-A804 (lanes 3 and 4), gRNA-A805 (lanes 5 and 6), gRNA-A806 (lanes 7 and 8), gRNA-U809 (lanes 9 and 10), gRNA-A810 (lanes 11 and 12) or gRNA-U811 (lanes 13 and 14) was used for primer-extension analysis in the presence of high (H; 1 mM, odd-numbered lanes) or low (L; 0.001 mM, even-numbered lanes) dNTP concentrations. Arrows indicate the stop/pause signals corresponding to the 2'-O-methylated residues. The TLC1 sequencing ladder is shown on the left. (C) The strategy behind ligation-based 2'-O-methylation assay (also see Methods and text). The thick lines represent the target RNA substrate, and the thin lines stand for primer pairs (ND, non-discriminating; D, discriminating) used for ligation. N denotes a test nucleotide lacking 2'-O-methylation; Nm represents a test nucleotide that is 2'-O-methylated. Nicks (on the 5' or 3' side of the test nucleotide) are also shown. (D) Ligation-based quantification of 2'-O-methylation. RNA was isolated from cells after 30 generations that expressed a random (control) gRNA (lanes 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21 and 22), gRNA-A804 (lanes 3 and 4), gRNA-A805 (lanes 7 and 8), gRNA-A806 (lanes 11 and 12), gRNA-U809 (lanes 15 and 16), gRNA-A810 (lanes 19 and 20) or gRNA-U811 (lanes 23 and 24) and assayed for 2'-O-methylation at the respective positions with position specific primer pairs (A804, lanes 1-4; A805, lanes 5-8; A806, lanes 9-12; U809, lanes 13-16; A810, lanes 17-20; U811, lanes 21-24). D, discriminating primer pair (odd numbered lanes); N, non-discriminating primer pair (even-numbered lanes). In all lanes, an additional pair of labeled primers was also included for a loading control. The relative modification efficiencies are calculated and shown in parentheses. (E) As in (D) except that RNA was isolated from cells after 590 generations.

FIG. 3 shows experimental results demonstrating that 2%-O-methylated TLC1 RNA is incorporated into telomerase RNP. (A) 2'-Omethylation has no effect on the steady-state level of TLC1 RNA. Cells expressing a random gRNA (control; lane 1), gRNA-A804 (lane 2), gRNA-A805 (lane 3), gRNA-A806 (lane 4), gRNA-U809 (lane 5), gRNA-A810 (lane 6) or gRNA-U811 (lane 7), were grown for 30 generations (top panel), 310 generations (middle panel), and 590 generations (bottom panel). RNAs were isolated from these cells and analyzed by northern blotting with TLC1-specific and U1-specific probes. TLC1 RNA levels were calculated relative to U1 (in percentage). (B) Incorporation of TLC1 RNA into telomerase RNP. Extracts prepared from cells expressing a random gRNA (control; top panel) or gRNA-U809 were loaded on a 15-40% glycerol gradient. Nineteen fractions were collected. RNA from each fraction was analyzed by northern blotting with TLC1-specific and U1-specific probes. On the right is a plot showing the TLC1 and U1 signal peaks. (C) Fractions 12-15 of the gradient described in (B) were pooled, RNAs were recovered, and primer extension

5

was carried out in the presence of high (H; lanes 1 and 3) or low (L; lanes 2 and 4) dNTP concentrations. Lanes 1 and 2 are from cells expressing a random gRNA (control), and lanes 3 and 4 are from cells expressing gRNA-U809. A TLC sequencing ladder was electrophoresed in parallel on the left. A signal corresponding to 2%-methylated U809 is indicated. (D) Western and northern analyses of immunoprecipitated Est2p complex. A yeast strain, in which EST2 gene is fused with a protein A tag, was transformed with a plasmid containing no gRNA (lane 8), a random (control) gRNA (lane 1), gRNA-A804 (lane 2), gRNA-A805 (lane 3), gRNA-A806 (lane 4), gRNA-U809 (lane 5), gRNA-A810 (lane 6) or gRNA-U811 (lane 7). IgG precipitation was subsequently carried out. As a control, an untagged yeast strain was also used for IgG precipitation (lane 9). Precipitated proteins were recovered, and western analysis (with anti-protein A antibodies) performed. Furthermore, RNA co-precipitated with protein A-Est2p was recovered, and northern analysis carried out. Probes for U1 (loading control) and TLC1 were used, and signals corresponding to these RNAs are indicated. As a control, total cellular RNA was also used (lane 10). (E) 2'-O-methylation mapping was conducted as in (C). All seven samples [corresponding to lanes 1-7 in (D)] were assayed.

FIG. 4 shows the experimental results demonstrating of an in vitro telomerase activity assay. (A) IgG-bound (protein A-Est2p) fraction described in FIG. 3D was used directly for in vitro telomerase activity assay (Seto, A. G., et al., *Rna* 9:1323-32 (2003)). Three independent sets of experiments, each in duplicate, were carried out. Shown is one such experiment. Duplicate lanes represent two independent reactions for each strain. A control band [for recovery and loading control (Seto, A. G., et al., *Nature* 401:177-80 (1999))] is also shown. (B) Relative telomerase activity of the IgG-bound fraction, derived from each strain, was quantified based on three independent sets of duplicate experiments. The quantification was performed by comparing the intensity of the bands (the sum of all seven bands) in each lane. Adjustment was made for every band by deducting a background area immediately above the band. Percentage of in vitro telomerase activity of each strain was calculated against control activity (set to 100%). The error bars represent the standard deviation of the measurements. Asterisks (*) indicate that the P-values are less than 0.05 (calculated using the Microsoft Excel t-test software).

FIG. 5 shows Southern analysis of chromosome end length in cells expressing various artificial guide RNAs. Cells (yCH-002) expressing a random gRNA (control; lanes 1-6); gRNA-A804 (lanes 7-12); gRNA-A805 (lanes 13-18), gRNA-A806 (lanes 19-24), gRNA-U809 (lanes 25-32), gRNA-A810 (lanes 33-38) or gRNA-U811 (lanes 39-44), were harvested after growing for the indicated number of generations (G#). DNA was recovered, digested with XbaI and hybridized with two radiolabeled probes, a telomere-specific one and a chromosome IV-specific one (as an internal control). The fragment of chromosome IV (Chr4) and the telomeres (TRF) are indicated. For each strain, two independent experiments are presented in duplicate lanes. The distances between the signal peaks of Chr4 and TRF were measured using Imagequant software (Molecular Dynamics) (Bachellerie, J. P., et al., *Trends Biochem. Sci.* 20:261-4 (1995)). Shown in parentheses at the top of each strain are the relative changes in distance between two time points (30 and 590 generations) (difference in average distance between the two time points, divided by the average distance at 30 generations). “+” indicates telomere lengthening, and “-” indicates telomere shortening.

FIG. 6 shows the experimental results of a telomere position effect assay. (A) Cells (yCH-002) expressing a random

6

gRNA (control), gRNA-A804, gRNA-A805, gRNA-A806, gRNA-U809, gRNA-A810 or gRNA-U811 were grown for the indicated number of generations and then plated on SD-Leu medium with or without 5-FOA. (B) DNAs were recovered from the cells described in (A), cleaved with PstI and hybridized with a URA3-specific radiolabeled probe and a chromosome IV—specific radiolabeled probe. Left panel: the schematic shows the modified chromosome VII with URA3 inserted near the telomere. A PstI site and the site of hybridization with the URA3 probe (a thick line with a star) are indicated. Right panel: the signals corresponding to the chromosome IV fragment and the telomere of chromosome VII are indicated.

FIG. 7 shows an alignment of a portion of the telomerase RNA from vertebrates showing part of the pseudoknot region of the telomerase RNA. The alignment is taken from the Telomerase Database (telomere.asu.edu: Podlevsky, J D., et al., *Nucleic Acids Research* 36 (database issue):D339-D343 (2008)).

DETAILED DESCRIPTION

Definitions

Unless otherwise expressly defined, the terms used herein are to be understood according to their ordinary meaning in the art. Terms used in the singular or referred to as “a” or “an” also include the plural and vice versa, unless otherwise specified or indicated by context. Standard techniques and procedures are generally performed according to conventional methods in the art and various general references (see generally, Sambrook et al. *Molecular Cloning: A Laboratory Manual*, 2nd ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., which is incorporated herein by reference), which are provided throughout this document. The disclosures of the references cited in this document are all incorporated herein by reference.

As used herein, the term “Small nucleolar RNAs (snoRNAs)” refers to a class of small non-coding RNA molecules that primarily guide chemical modifications of other RNAs, mainly ribosomal RNAs, transfer RNAs and small nuclear RNAs. There are two main classes of snoRNA, the C/D box snoRNAs which are associated with methylation modifications and H/ACA box snoRNAs which are associated with pseudouridylation modifications. snoRNAs may be represented herein as a RNA nucleic acid sequence or as a DNA nucleic acid sequence encoding the RNA nucleic acid sequence.

As used herein, the term “guide sequence” refers to a nucleic acid sequence of a snoRNA which base pairs with a target RNA molecule to guide modification of the target molecule.

As used herein, the term “engineered snoRNA” refers to a RNA for which part of the native sequence has been modified. In certain examples, engineered snoRNAs have the native guide sequence replaced with an engineered guide sequence that causes the snoRNA to target RNA modification at a specific position in the target RNA.

As used herein, the term “target RNA” or “target RNA molecule” refers to any RNA in which a modification is effected by contacting the target RNA with a snoRNA.

As used herein, the term “telomerase ribonucleoprotein complex” refers to the enzymatically functional complex of telomerase ribonucleoproteins and telomerase RNA.

As used herein, the term “telomerase RNA” or “telomerase RNA component” refers to the non-coding RNA molecule that is present in the telomerase ribonucleoprotein complex.

As used herein, the terms “altering,” “modulating,” or “modifying,” as they relate to telomerase activity, refer to a difference in the enzymatic activity of the telomerase ribonucleoprotein complex containing a modified telomerase RNA, e.g., a telomerase ribonucleoprotein complex containing telomerase RNA having a modified nucleotide that is not present in the native telomerase RNA, when compared with the enzymatic activity of a native (wild type) telomerase, e.g., a telomerase ribonucleoprotein complex containing native telomerase RNA. A telomerase ribonucleoprotein may have increased or decreased enzymatic activity compared to wild type within the meaning of this term.

The present invention provides methods and C/D box small nucleolar RNAs (snoRNAs), or guide RNAs, that allow for the alteration of telomerase enzymatic activity and, subsequently, telomerase length. The methods of the present invention involve targeting the 2'-O-methylation modification of nucleotides in a pseudoknot region of the telomerase RNA, see, e.g., (FIG. 1A).

As is exemplified herein, 2'-O-methylation of nucleotides in a pseudoknot region of the telomerase RNA results in changes in telomere length. In certain embodiments, modification of a nucleotide at a specific position in the telomerase RNA causes reduced or decreased telomerase activity, resulting in telomere shortening. In other embodiments, modification of a nucleotide at a specific position in the telomerase RNA causes increased telomerase activity, resulting in telomere lengthening.

The present invention contemplates the use of C/D box snoRNAs for the targeted 2'-O-methylation of the telomerase RNA component. C/D box snoRNAs are known in the art. It is known that target RNA 2'-O-methylation always occurs in the residue base-paired to the nucleotide in snoRNA precisely 5 nucleotides upstream from box D (or D') (FIG. 1B) (Kiss-Laszlo, Z., et al., *Cell* 85:1077-88 (1996); Balakin, et al., *Cell* 86:823-34 (1996); Cavaille, J., M. et al., *Nature* 383:732-5 (1996)). Once the box C/D snoRNA finds its nucleotide target, fibrillarin, a methyl-transferase associated with the box C/D guide RNA, delivers the methyl group to the target nucleotide at the 2'-O position. The “Box D+5 rule” for predicting the site of 2'-O-methylation guided by snoRNAs has since been confirmed in various organisms including yeast, *Xenopus* and human (Smith, C. M., et al., *Cell* 89:669-72 (1997); Peculis, B., *Curr. Biol.* 7:R480-2 (1997); Kiss, T. et al., *Embo J* 20:3617-22 (2001); Kiss, T., et al., *Cell* 109:145-8 (2001)). Most Box D or D' sequences are CUGA while some less conserved Box D or D' sequences may be AUGA as is well known to a person of skill in the art.

The present invention provides a novel, improved way to regulate telomerase activity. Over the years, a number of different strategies have been developed for up- or down-regulating telomerase activity in various organisms. Among them, the antisense RNA approach and RNA interference (RNAi) to regulate mammalian telomerase activity have drawn a great deal of attention. Although well conceptualized, the antisense RNA approach is effective for only a few cases, and most trials have failed for a number of reasons.

One of the most important reasons for the failure of antisense RNA trials is the instable nature of a foreign antisense RNA when introduced into cells. Usually, the antisense RNA is significantly degraded before reaching its target. The development of RNAi strategies has changed the way gene silencing can be achieved. Using the RNAi strategies, several labs have knocked down telomerase RNA, the protein components of telomerase RNP, or proteins that are relevant to telomerase function, thus inhibiting telomerase activity (Wang, Y., et al., *Cancer Biol. Ther.* 7(6):896-901 (2008);

Chen, S. M., et al., *Cancer Biol. Ther.* 7(5):734-739 (2008); Kosciolek, B. A., et al., *Mol. Cancer Ther.* 2(3):209-16 (2003); Li, S., et al., *Cancer Res.* 64(14):4833-40 (2004); Patry, C., et al., *Cancer Res.* 63(22):7679-88 (2003); Cousens, M., et al., *Proc. Natl. Acad. Sci. USA* 107 (31): p. 13842-7 (2010)). In some cases, knockdown of proteins that negatively impact telomerase function (e.g., those that block telomerase recruitment to telomeres or suppress hTERT expression) can upregulate telomerase activity (Maurelli, R., et al., *FASEB J* 20(9):1516-8 (2006); Bazarov, A. V., et al., *Aging Cell* 9(5):736-46 (2010)). However, although convenient and widely used, the RNAi approach also has some limitations. For instance, the knock down of a gene usually requires many trials with different siRNAs—there are no exact rules for siRNA design. With regard to genes for which RNAi has an effect, they are usually just moderately “knocked down”. In at least some organisms reported (e.g., *C. elegans*), the RNAi effect is less specific, probably due to transitive RNAi by a secondary siRNA (Sijen, T., et al., *Cell* 107(4):465-76 (2001)).

In comparison, the use of RNA-guided modifications targeted to telomerase RNA is advantageous in many different ways. First, RNA-guided RNA modification is absolutely conserved across species, from yeast to humans (Yu, Y. T., et al., in H. Grosjean (Ed.): *Fine-Tuning of RNA Functions by Modification and Editing*, vol. 12, Springer-Verlag, Berlin Heidelberg (2005)). Thus, this approach is, in principle, applicable to all eukaryotes. Second, guide RNAs are stable in cells (Balakin, et al., *Cell* 86:823-34 (1996); Tykowski, K. T., et al., *Nature* 379(6564):464-6 (1996)). Just as their native counterparts, foreign guide RNAs, when introduced into cells, they are assembled into RNA-protein complexes that are stable presumably throughout the lifetime of cells, and possibly are even passed on to subsequent generations. Third, there are simple and clear rules for guide RNA design (Huang, C. et al., *Mol. Cell. Biol.* 30(18):4368-78 (2010)). To target different sites within telomerase RNA for modification, only the guide sequence of a guide RNA needs to be changed accordingly. Fourth, as shown in the examples below, modification is highly efficient—for a given site more than 70% of modification was observed. Fifth, based on a large amount of experimental evidence and experience (Huang, C. et al., *Mol. Cell. Biol.* 30(18):4368-78 (2010); Zhao, X. et al., *Nat. Methods* 5 (1): p. 95-100 (2008)). RNA-guided nucleotide 2'-O-methylation is extremely site-specific. Indeed, modification occurs only in the target site in telomerase RNA or in other RNA. Sixth, as shown in the examples below, depending on the sites to which 2'-O-methylation is targeted, telomerase activity can be either enhanced or inhibited, thus offering an opportunity to manipulate telomerase activity in both directions. Finally, targeted 2'-O-methylation also offers a unique opportunity to investigate the functionality of the RNA backbone (particularly, 2'-OH moieties) (Huang, C. et al., *Mol. Cell. Biol.* 30(18):4368-78 (2010); Zhao, X. et al., *Nat. Methods* 5 (1): p. 95-100 (2008)), which has proved to be difficult to study *in vivo* (mutation of the 2'-OH at the DNA level is impossible).

For the guided modification mechanisms of the present invention, the snoRNA guide sequences can be modified to base pair with a sequence of the target telomerase RNA adjacent to the nucleotide to be modified. The engineered snoRNA guide sequences should be made to base pair with the appropriate sequence in the target RNA so that the nucleotide is in the proper position to undergo modification.

The present invention contemplates the use of C/D box snoRNAs engineered to effect a 2'-O-methylation modifica-

tion at a specific position of the subject telomere RNA. C/D box RNAs vary across species, but all allow for 2'-O-modification at the “Box D+5” position. Therefore, C/D box snoRNAs from various species may be targeted to a specific residue by placing a guide sequence upstream of Box D of the snoRNA so that the residue to be modified is 5 nucleotides upstream from Box D. For example, in the case of most snoRNAs, the residue to be modified is 5 nucleotides upstream from the C of the CUGA Box D sequence. With this method, almost any C/D box snoRNA may be engineered to effect 2'-O-methyl modification of a selected base in a target telomerase RNA.

One of skill in the art will recognize that almost any human C/D box snoRNA may be used in the present invention. Examples of nucleic acids encoding human C/D box snoRNAs that may be modified for use with the present invention, named according to the HUGO Gene Nomenclature Committee convention, include: SNORD 14A (SEQ ID NO: 1), SNORD 14B (SEQ ID NO: 2), SNORD 15A (SEQ ID NO: 3), SNORD 15B (SEQ ID NO: 4), SNORD 16 (SEQ ID NO: 5), SNORD 17 (SEQ ID NO: 6), SNORD 18A (SEQ ID NO: 7), SNORD 18B (SEQ ID NO: 8), SNORD 18C (SEQ ID NO: 9), SNORD 19 (SEQ ID NO: 10), SNORD 19B (SEQ ID NO: 11), SNORD 20 (SEQ ID NO: 12), SNORD 21 (SEQ ID NO: 13), SNORD 22 (SEQ ID NO: 14), SNORD 23 (SEQ ID NO: 15), SNORD 24 (SEQ ID NO: 16), SNORD 25 (SEQ ID NO: 17), SNORD 26 (SEQ ID NO: 18), SNORD 27 (SEQ ID NO: 19), SNORD 28 (SEQ ID NO: 20), SNORD 29 (SEQ ID NO: 21), SNORD 30 (SEQ ID NO: 22), SNORD 31 (SEQ ID NO: 23), SNORD 32A (SEQ ID NO: 24), SNORD 32B (SEQ ID NO: 25), SNORD 34 (SEQ ID NO: 26), SNORD 35A (SEQ ID NO: 27), SNORD 35B (SEQ ID NO: 28), SNORD 36A (SEQ ID NO: 29), SNORD 36B (SEQ ID NO: 30), SNORD 36C (SEQ ID NO: 31), SNORD 37 (SEQ ID NO: 32), SNORD 38A (SEQ ID NO: 33), SNORD 38B (SEQ ID NO: 34), SNORD 41 (SEQ ID NO: 35), SNORD 42A (SEQ ID NO: 36), SNORD 42B (SEQ ID NO: 37), SNORD 43 (SEQ ID NO: 38), SNORD 44 (SEQ ID NO: 39), SNORD 45A (SEQ ID NO: 40), SNORD 45B (SEQ ID NO: 41), SNORD 45C (SEQ ID NO: 42), SNORD 46 (SEQ ID NO: 43), SNORD 47 (SEQ ID NO: 44), SNORD 48 (SEQ ID NO: 45), SNORD 49A (SEQ ID NO: 46), SNORD 49B (SEQ ID NO: 47), SNORD 50 (SEQ ID NO: 48), SNORD 50B (SEQ ID NO: 49), SNORD 51 (SEQ ID NO: 50), SNORD 52 (SEQ ID NO: 51), SNORD 53 (SEQ ID NO: 52), SNORD 54 (SEQ ID NO: 53), SNORD 56 (SEQ ID NO: 54), SNORD 57 (SEQ ID NO: 55), SNORD 58A (SEQ ID NO: 56), SNORD 58B (SEQ ID NO: 57), SNORD 58C (SEQ ID NO: 58), SNORD 59A (SEQ ID NO: 59), SNORD 59B (SEQ ID NO: 60), SNORD 60 (SEQ ID NO: 61), SNORD 61 (SEQ ID NO: 62), SNORD 62A (SEQ ID NO: 63), SNORD 62B (SEQ ID NO: 64), SNORD 63 (SEQ ID NO: 65), SNORD 64 (SEQ ID NO: 66), SNORD 65 (SEQ ID NO: 67), SNORD 66 (SEQ ID NO: 68), SNORD 67 (SEQ ID NO: 69), SNORD 69 (SEQ ID NO: 70), SNORD 70 (SEQ ID NO: 71), SNORD 71 (SEQ ID NO: 72), SNORD 72 (SEQ ID NO: 73), SNORD 73A (SEQ ID NO: 74), SNORD 73B (SEQ ID NO: 75), SNORD 74 (SEQ ID NO: 76), SNORD 75 (SEQ ID NO: 77), SNORD 76 (SEQ ID NO: 78), SNORD 77 (SEQ ID NO: 79), SNORD 78 (SEQ ID NO: 80), SNORD 79 (SEQ ID NO: 81), SNORD 80 (SEQ ID NO: 82), SNORD 81 (SEQ ID NO: 83), SNORD 82 (SEQ ID NO: 84), SNORD 83A (SEQ ID NO: 85), SNORD 83A (SEQ ID NO: 86), SNORD 84 (SEQ ID NO: 87), SNORD 85 (SEQ ID NO: 88), SNORD 86 (SEQ ID NO: 89), SNORD 87 (SEQ ID NO: 90), SNORD 88A (SEQ ID NO: 91), SNORD 88B (SEQ ID NO: 92), SNORD 88C (SEQ ID NO: 93), SNORD 89 (SEQ ID NO: 94), SNORD 90 (SEQ ID NO: 95),

SNORD91A (SEQ ID NO: 96), SNORD91B (SEQ ID NO: 97), SNORD 92 (SEQ ID NO: 98), SNORD 93 (SEQ ID NO: 99), SNORD 94 (SEQ ID NO: 100), SNORD 95 (SEQ ID NO: 101), SNORD 96A (SEQ ID NO: 102), SNORD 96B (SEQ ID NO: 103), SNORD 97 (SEQ ID NO: 104), SNORD 98 (SEQ ID NO: 105), SNORD 99 (SEQ ID NO: 106), SNORD 100 (SEQ ID NO: 107), SNORD 101 (SEQ ID NO: 108), SNORD 102 (SEQ ID NO: 109), SNORD 103A (SEQ ID NO: 110), SNORD 103B (SEQ ID NO: 111), SNORD 104 (SEQ ID NO: 112), SNORD 105A (SEQ ID NO: 113), SNORD 105B (SEQ ID NO: 114), SNORD 107 (SEQ ID NO: 115), SNORD 108 (SEQ ID NO: 116), SNORD 109A (SEQ ID NO: 117), SNORD 109B (SEQ ID NO: 118), SNORD 110 (SEQ ID NO: 119), SNORD 111A (SEQ ID NO: 120), SNORD 111B (SEQ ID NO: 121), SNORD 112 (SEQ ID NO: 122), SNORD 113-1 (SEQ ID NO: 123), SNORD 113-2 (SEQ ID NO: 124), SNORD 113-3 (SEQ ID NO: 125), SNORD 113-4 (SEQ ID NO: 126), SNORD 113-5 (SEQ ID NO: 127), SNORD 113-6 (SEQ ID NO: 128), SNORD 113-7 (SEQ ID NO: 129), SNORD 113-8 (SEQ ID NO: 130), SNORD 113-9 (SEQ ID NO: 131), SNORD 114-1 (SEQ ID NO: 132), SNORD 114-2 (SEQ ID NO: 133), SNORD 114-3 (SEQ ID NO: 134), SNORD 114-4 (SEQ ID NO: 135), SNORD 114-5 (SEQ ID NO: 136), SNORD 114-6 (SEQ ID NO: 137), SNORD 114-7 (SEQ ID NO: 138), SNORD 114-8 (SEQ ID NO: 139), SNORD 114-9 (SEQ ID NO: 140), SNORD 114-10 (SEQ ID NO: 141), SNORD 114-11 (SEQ ID NO: 142), SNORD 114-12 (SEQ ID NO: 143), SNORD 114-13 (SEQ ID NO: 144), SNORD 114-14 (SEQ ID NO: 145), SNORD 114-15 (SEQ ID NO: 146), SNORD 114-16 (SEQ ID NO: 147), SNORD 114-17 (SEQ ID NO: 148), SNORD 114-18 (SEQ ID NO: 149), SNORD 114-19 (SEQ ID NO: 150), SNORD 114-20 (SEQ ID NO: 151), SNORD 114-21 (SEQ ID NO: 152), SNORD 114-22 (SEQ ID NO: 153), SNORD 114-23 (SEQ ID NO: 154), SNORD 114-24 (SEQ ID NO: 155), SNORD 114-25 (SEQ ID NO: 156), SNORD 114-26 (SEQ ID NO: 157), SNORD 114-27 (SEQ ID NO: 158), SNORD 114-28 (SEQ ID NO: 159), SNORD 114-29 (SEQ ID NO: 160), SNORD 114-30 (SEQ ID NO: 161), SNORD 114-31 (SEQ ID NO: 162), SNORD 116-1 (SEQ ID NO: 163), SNORD 116-2 (SEQ ID NO: 164), SNORD 116-3 (SEQ ID NO: 165), SNORD 116-4 (SEQ ID NO: 166), SNORD 116-5 (SEQ ID NO: 167), SNORD 116-7 (SEQ ID NO: 168), SNORD 116-8 (SEQ ID NO: 169), SNORD 116-9 (SEQ ID NO: 170), SNORD 116-10 (SEQ ID NO: 171), SNORD 116-11 (SEQ ID NO: 172), SNORD 116-12 (SEQ ID NO: 173), SNORD 116-13 (SEQ ID NO: 174), SNORD 116-14 (SEQ ID NO: 175), SNORD 116-15 (SEQ ID NO: 176), SNORD 116-16 (SEQ ID NO: 177), SNORD 116-17 (SEQ ID NO: 178), SNORD 116-18 (SEQ ID NO: 179), SNORD 116-19 (SEQ ID NO: 180), SNORD 116-20 (SEQ ID NO: 181), SNORD 116-21 (SEQ ID NO: 182), SNORD 116-22 (SEQ ID NO: 183), SNORD 116-23 (SEQ ID NO: 184), SNORD 116-24 (SEQ ID NO: 185), SNORD 116-25 (SEQ ID NO: 186), SNORD 116-26 (SEQ ID NO: 187), SNORD 116-27 (SEQ ID NO: 188), SNORD 116-28 (SEQ ID NO: 189), SNORD 116-29 (SEQ ID NO: 190), SNORD 116-6 (SEQ ID NO: 191), SNORD 117 (SEQ ID NO: 192), SNORD 118 (SEQ ID NO: 193), SNORD 119 (SEQ ID NO: 194), SNORD 121A (SEQ ID NO: 195), SNORD 121B (SEQ ID NO: 196), SNORD 123 (SEQ ID NO: 197), SNORD 124 (SEQ ID NO: 198), SNORD 125 (SEQ ID NO: 199), SNORD 126 (SEQ ID NO: 200), SNORD 127 (SEQ ID NO: 201), SNORD 2 (SEQ ID NO: 202), SNORD 3 (SEQ ID NO: 203), SNORD 3-2 (SEQ ID NO: 2 (4)), SNORD 3-2B (SEQ ID NO: 205), SNORD 3-3 (SEQ ID NO: 206), SNORD 3-4 (SEQ ID NO: 207), SNORD

4A (SEQ ID NO: 208), SNORD 4B (SEQ ID NO: 209), SNORD 5 (SEQ ID NO: 210), SNORD 6 (SEQ ID NO: 211), SNORD 7 (SEQ ID NO: 212), SNORD 8 (SEQ ID NO: 213), SNORD 9 (SEQ ID NO: 214), SNORD 10 (SEQ ID NO: 215), SNORD 11 (SEQ ID NO: 216), SNORD 12 (SEQ ID NO: 217), SNORD 12B (SEQ ID NO: 218), SNORD 12 (SEQ ID NO: 219), SNORD 13 (SEQ ID NO: 220), SNORD115-1 (SEQ ID NO: 366), SNORD115-2 (SEQ ID NO: 367), SNORD115-3 (SEQ ID NO: 368), SNORD115-4 (SEQ ID NO: 369), SNORD115-5 (SEQ ID NO: 370), SNORD115-6 (SEQ ID NO: 371), SNORD115-7 (SEQ ID NO: 372), SNORD115-8 (SEQ ID NO: 373), SNORD115-9 (SEQ ID NO: 374), SNORD115-10 (SEQ ID NO: 375), SNORD115-11 (SEQ ID NO: 376), SNORD115-12 (SEQ ID NO: 377), SNORD115-13 (SEQ ID NO: 378), SNORD115-14 (SEQ ID NO: 379), SNORD115-15 (SEQ ID NO: 380), SNORD115-16 (SEQ ID NO: 381), SNORD115-17 (SEQ ID NO: 382), SNORD115-18 (SEQ ID NO: 383), SNORD115-19 (SEQ ID NO: 384), SNORD115-20 (SEQ ID NO: 385), SNORD115-21 (SEQ ID NO: 386), SNORD115-22 (SEQ ID NO: 387), SNORD115-23 (SEQ ID NO: 388), SNORD115-25 (SEQ ID NO: 389), SNORD115-26 (SEQ ID NO: 390), SNORD115-29 (SEQ ID NO: 391), SNORD115-30 (SEQ ID NO: 392), SNORD115-31 (SEQ ID NO: 393), SNORD115-32 (SEQ ID NO: 394), SNORD115-33 (SEQ ID NO: 395), SNORD115-34 (SEQ ID NO: 396), SNORD115-35 (SEQ ID NO: 397), SNORD115-36 (SEQ ID NO: 398), SNORD115-37 (SEQ ID NO: 399), SNORD115-38 (SEQ ID NO: 400), SNORD115-39 (SEQ ID NO: 401), SNORD115-40 (SEQ ID NO: 402), SNORD115-41 (SEQ ID NO: 403), SNORD115-42 (SEQ ID NO: 404), SNORD115-43 (SEQ ID NO: 405), SNORD115-44 (SEQ ID NO: 406), SNORD115-48 (SEQ ID NO: 407), SNORD 33 (SEQ ID NO: 408), SNORD 55 (SEQ ID NO: 409), SNORD 68 (SEQ ID NO: 410), or analogues thereof, e.g., a nucleic acid or polynucleotide comprising an nucleic acid sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a known snoRNA sequence.

More information on human C/D box snoRNAs may be found in the LMBe snoRNABase database, which is available at www-snorna.bioutoul.fr (see, Lestrade, L., and Weber, M. J. *Nucleic Acids Res.* 34 (database issue): D158-162 (2006)), as well as other databases which are well known to a person of skill in the art, such as the rFam database (rfam.sanger.ac.uk; see, P. P. Gardner, et al., *Nucleic Acids Res.* doi: 10.1093/nar/gkq1129 (2011)). The snoRNABase lists the location of the D and/or D' Box and the native guide sequences in each snoRNA, allowing for a person of skill in the art to easily locate the Box D+5 position and engineer a snoRNA for specific targeting of residues for 2'-O-methyl modification.

Many of the human C/D box snoRNAs listed above have homologs in other vertebrate species, which may also be engineered accord to the invention, including: *Macaca mulatta* (rhesus monkey), *Sus scrofa* (pig), *Danio rerio* (zebrafish), *Loxodonta africana* (African savanna elephant), *Lama pacos* (alpaca), *Cavia porcellus* (domestic guinea pig), *Bos taurus* (cattle), *Canis lupus familiaris* (dog), *Pan troglodytes* (chimpanzee), *Pongo abelii* (Sumatran orangutan), *Gorilla gorilla gorilla* (Western lowland gorilla), *Gorilla gorilla* (Western Gorilla), *Equus caballus* (horse), *Tursiops truncatus* (bottlenosed dolphin), *Myotis lucifugus* (little brown bat), *Oryctolagus cuniculus* (rabbit), *Felis catus* (domestic cat), *Rattus norvegicus* (Norway rat), *Mus musculus* (house mouse) and *Xenopus laevis* (African clawed frog). Additional snoRNAs contemplated include those from: *Danio rerio* (zebrafish); invertabrates: *Ciona intestinalis* (sea

squirt), *Ciona savignyi* (sea squirt), *Strongylocentrotus purpuratus* (purple sea urchin), *Gammarus pulex* (freshwater shrimp), *Drosophila melanogaster* (fruit fly), *Drosophila virilis* (fly), *Chironomus tentans* (fly), *Anopheles gambiae* (African malaria mosquito), *Sialis lutaria* (alderfly), *Apis mellifera* (honey bee), *Bombyx mori* (domestic silkworm), *Bombyx mandarina* (wild silkworm), *Papilio xuthus* (butterfly), *Hodotermopsis japonicus* (termite), *Periplaneta fuliginosa* (dusky-brown cockroach), *Tapinoma nigerrimum* (ant), *Manica yessensis* (ant), *Myrmecia* sp. (ant); Nematodes: *Ascaris lumbricoides* (common roundworm), *Ascaris suum* (pig round worm), *Parascaris univalens*, *Caenorhabditis elegans*; Fungi: *Schizosaccharomyces pombe* (fission yeast), *Saccharomyces cerevisiae* (baker's yeast), *Saccharomyces pastorianus* (lager yeast), *Saccharomyces kluyveri*, *Kluyveromyces lactis*, *Candida albicans*, *Pichia guilliermondii*, *Pichia stipites*, *Aspergillus fumigatus*, *Aspergillus oryzae*, *Aspergillus niger* and *Neurospora crassa*. It is also contemplated that analogs of such C/D box snoRNAs may be used such as nucleic acids comprising an nucleic acid sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a known snoRNA sequence for each C/D box snoRNA listed above. Examples of such homologs may be found in the rFam database. As the Box D sequence is highly conserved among species and typically has the sequence CUGA or AUGA, a person of skill in the art can locate the D and/or D' Box and the native guide sequences in homolog snoRNAs. This allows for a person of skill in the art to easily locate the Box D+5 position and engineer a snoRNA for specific targeting of residues for 2'-O-methyl modification.

Still further examples of C/D box snoRNAs known in the art include the *Saccharomyces cerevisiae* snoRNAs: U14 (SEQ ID NO: 221), U18 (SEQ ID NO: 222), U24 (SEQ ID NO: 223), snR4 (SEQ ID NO: 224), snR13 (SEQ ID NO: 225), snR38 (SEQ ID NO: 226), snR39 (SEQ ID NO: 227), snR39b (SEQ ID NO: 228), snR40 (SEQ ID NO: 229), snR41 (SEQ ID NO: 230), snR45 (SEQ ID NO: 231), snR47 (SEQ ID NO: 232), snR48 (SEQ ID NO: 233), snR50 (SEQ ID NO: 234), snR51 (SEQ ID NO: 235), snR52 (SEQ ID NO: 236), snR53 (SEQ ID NO: 237), snR54 (SEQ ID NO: 238), snR55 (SEQ ID NO: 239), snR56 (SEQ ID NO: 240), snR57 (SEQ ID NO: 241), snR58 (SEQ ID NO: 242), snR59 (SEQ ID NO: 243), snR60 (SEQ ID NO: 244), snR61 (SEQ ID NO: 245), snR62 (SEQ ID NO: 246), snR63 (SEQ ID NO: 247), snR64 (SEQ ID NO: 248), snR65 (SEQ ID NO: 249), snR66 (SEQ ID NO: 250), snR67 (SEQ ID NO: 251), snR68 (SEQ ID NO: 252), snR69 (SEQ ID NO: 253), snR70 (SEQ ID NO: 254), snR71 (SEQ ID NO 255), snR72 (SEQ ID NO: 256), snR73 (SEQ ID NO: 257), snR74 (SEQ ID NO: 258), snR75 (SEQ ID NO: 259), snR76 (SEQ ID NO: 260), snR77 (SEQ ID NO: 261), snR78 (SEQ ID NO: 262), snR79 (SEQ ID NO: 263), snR87 (SEQ ID NO 264), snR190 (SEQ ID NO: 265) or analogues thereof, e.g., a nucleic acid or polynucleotide comprising an nucleic acid sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a known snoRNA sequence. Further information on the above listed snoRNAs and other C/D box snoRNAs can be found in the UMASS Amherst Yeast snoRNA database (people.biochem.umass.edu/sfournier/fournierlab/snornadb/main.php, see, D. Pieckna-Przybylska, et al., *Rna* 13(3):305-12)(2007)). Telomerase Target RNAs

The target RNA molecules of the present invention comprise a telomerase RNA, for example, TR (or TERC) in humans. Examples of nucleic acids encoding telomerase RNAs that are suitable targets for the present invention are listed in the Telomerase Database (telomerase.asu.edu, see, Podlevsky, J. D., et al., *Nucleic Acids Res.* 36 (database issue):

13

D339-D343(2008)). Examples of nucleic acids encoding telomerase RNA that may be targeted in the present invention include: vertebrates: *Homo sapiens* (human) (SEQ ID NO: 266), *Oryctolagus cuniculus* (domestic rabbit) (SEQ ID NO: 267), *Cavia porcellus* (domestic guinea pig) (SEQ ID NO: 268), *Cricetulus griseus* (Chinese hamster) (SEQ ID NO: 269), *Mus musculus* (mouse) (SEQ ID NO: 270), *Rattus norvegicus* (Norway rat) (SEQ ID NO: 271), *Felis catus* (cat) (SEQ ID NO: 272), *Bos taurus* (cattle) (SEQ ID NO: 273), *Sus scrofa* (pig) (SEQ ID NO: 274), *Equis caballus* (domestic horse) (SEQ ID NO: 275), *Elephas maximus* (Asian elephant) (SEQ ID NO: 276), *Gallus gallus* (chicken) (SEQ ID NO: 277), *Bombina japonica* (toad) (SEQ ID NO: 278), *Xenopus laevis* (African clawed frog) (SEQ ID NO: 279), *Danio rerio* (zebrafish) (SEQ ID NO: 280); Fungi: *Schizosaccharomyces pombe* (fission yeast) (SEQ ID NO: 281), *Saccharomyces cerevisiae* (baker's yeast) (SEQ ID NO: 282), *Saccharomyces pastorianus* (lager yeast) (SEQ ID NO: 283). *Candida albicans* (SEQ ID NO: 284), or analogues thereof, e.g., a nucleic acid or polynucleotide comprising an nucleic acid sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a known telomerase RNA sequence.

Telomerase RNA has a triple-helix as part of a pseudoknot structure that has been shown to be conserved and important to catalysis (Shefer, K., et al., *Mol. Cell Biol.* 27:2130-43 (2007); Qiao, F., et al., *Nat. Struct. Mol. Biol.* 15:634-40 (2008)). In certain embodiments, C/D box snoRNAs are engineered to effect 2'-O-methylation modification on a nucleotide in the pseudoknot region of the telomerase RNA. The structures and sequences for the telomerase RNAs of the present invention are available to one of skill in the art in the literature, for instance in the Telomerase Database (telomerase.asu.edu/structures.html). From review of the structure and sequence information, one of skill in the art will be able to engineer a C/D box snoRNA having a guide sequence that guides the 2'-O-methylation modification of the desired nucleotide, i.e., the nucleotide complementary to the C/D snoRNA nucleotide 5 bases upstream from the D or D box of the snoRNA.

For example, in certain embodiments, modifications to human telomerase RNA are made at one or more of positions 171-191 of SEQ ID NO: 266, which is a region near the pseudoknot of the telomerase RNA. This region is highly conserved among vertebrates, and typically has a sequence of five or more adenosine residues follow by the sequence UGUC or CGUC. An alignment of this region of the telomerase RNA, taken from the Telomerase Database, is shown in FIG. 7. From this alignment, a person of skill in the art would be able to determine which residues in the pseudoknot region may be modified according to the invention. For example, a person of skill in the art would recognize conserved sequences at positions 156-176 of mouse telomerase RNA (SEQ ID NO: 270), at positions 140-170 of rat telomerase

14

RNA (SEQ ID NO: 271), at positions 339-368 of xenopus telomerase RNA (SEQ ID NO: 279), along with other conserved regions.

It is further contemplated that any nucleotide within the target telomerase RNA may be modified using the methods of the present invention, using the structural information that is available in the art. Methods of creating libraries of snoRNA genes for modification at various positions within a target RNA are known in the art (Liu, B., J. Ni, and M. J. Fournier, "Probing RNA *in vivo* with methylation guide small nucleolar RNAs," *Methods*, 2001. 23 (3): p. 276-86).

Engineered snoRNAs

The engineered snoRNAs of the invention may be made using methods known in the art, see, e.g., (Liu, B., et al., *Methods* 23(3):276-86 (2001); Huang, C, et al., *Methods Mol. Biol.* 718:227-44 (2011)). In general, standard molecular biology techniques may be used to clone the native snoRNA gene, remove the guide sequence portion of the gene and replace the guide sequence with a guide sequence that targets 2'-O-methylation of a specific nucleotide on the target RNA. The cloned nucleic acids encoding engineered C/D box snoRNA may then be subcloned into vectors for replication of the cloned nucleic acid sequence and/or expression *in vivo*.

Expression of engineered snoRNAs *in vivo* may be effected by use of standard techniques known in the art. An engineered snoRNA can be produced *in vivo* in a mammal, e.g., a human patient, using gene therapy approaches known in the art. These approaches involve administration of a suitable engineered snoRNA encoding nucleic acid operably linked to suitable expression control sequences. Preferably, these sequences are incorporated into a viral vector. Suitable viral vectors for such *in vivo* expression include, e.g., adenoviral vectors, lentiviral vectors, baculoviral vectors, Epstein Barr viral vectors, papovaviral vectors, vaccinia viral vectors, herpes simplex viral vectors, and adeno associated virus (AAV) vectors. The viral vector can be a replication-defective viral vector. A preferred adenoviral vector has a deletion in its E1 gene or E3 gene. When an adenoviral vector is used, preferably, the mammal is not exposed to a nucleic acid encoding a selectable marker gene.

Expression of engineered snoRNAs in cell lines *in vivo* may also be performed using transformation, or injection methods known in the art for the cell line being used. See, for example, Huang, C, et al., *Methods Mol. Biol.* 718:227-44 (2011); 718:227-44 and Ge, J., et al., *Rna* 16:1078-1085 (2010). The nucleic acid sequences encoding the engineered snoRNAs may be cloned into vectors for expression in cells in the same manner as nucleic acid sequences encoding for proteins.

In certain embodiments, engineered snoRNAs are provided that direct 2'-O-methylation of nucleotides in or near the pseudoknot region of human telomerase RNA (SEQ ID NO: 266), positions 171-186 as highlighted:

```

1 GGGUUGCGGA GGGUGGGCCU GGGAGGGUG GUGGCCAUU UUUGUCUAAC CCUAACUGAG
61 AAGGGCGUAG GCGCCGUGCU UUUGCUCCCC CGCGCGUGUU UUUCUCGUG ACUUUCAGCG
121 GGC GGAAAAG CCUCGGCCUG CGCCUUCUCCA CGGUUCAUUC UAGAGCAAAC AAAAAAUGUC
181 ACCUUGCUGGC CGGUUCGCCU CUCCCCGGGA CCUGCGGGCG GUCGCCUGCC CAGCCCCCGA
241 ACCCCGCCUG GAGGCCGCGG UCGGCCCGGG GCUUCUCCGG AGGCACCCAC UGCCACCGCG
301 AAGAGUUGGG CUCUGUCAGC CGCGGGUCUC UCGGGGGCGA GGGCGAGGUU CAGGCCUUUC

```

-Continued

361 AGGCCGCAGG AAGAGGAACG GAGCGAGUCC CGCGCGCGG CGCGAUUCCC UGAGCUGUGG
 421 GACGUGCACC CAGGACUCGG CUCACACAUG C

5

Examples of nucleic acids encoding guide sequences upstream from the D box in a C/D box snoRNA (represented as the highlighted DNA sequence encoding the snoRNA) are shown below, with N representing any nucleotide. The guide sequences are engineered to modify the base complementary to the base shown in bold by their location upstream from Box D of the snoRNA. Guide sequences with and without the Box D sequence are shown for modification of each position below.

Guide Sequences and Box D Sequences:

15

(SEQ ID NO: 285)
 Position 171-**ACATTTTTGTTNCTGA**
 (SEQ ID NO: 286) 20
 Position 172-**GACATTTTTGTNCTGA**
 (SEQ ID NO: 287)
 Position 173-**TGACATTTTTGNCTGA**
 (SEQ ID NO: 288) 25
 Position 174-**CTGACATTTTTTNCTGA**
 (SEQ ID NO: 289)
 Position 175-**GCTGACATTTTNCTGA**
 (SEQ ID NO: 290) 30
 Position 176-**AGCTGACATTTTNCTGA**
 (SEQ ID NO: 291)
 Position 177-**CAGCTGACATTTNCTGA**
 (SEQ ID NO: 292) 35
 Position 178-**GCAGCTGACATTNCTGA**
 (SEQ ID NO: 293)
 Position 179-**TGCAGCTGACATNCTGA**
 (SEQ ID NO: 294) 40
 Position 180-**CTGCAGCTGACANCTGA**
 (SEQ ID NO: 295)
 Position 181-**CCTGCAGCTGACNCTGA**
 (SEQ ID NO: 296) 45
 Position 182-**GCCTGCAGCTGANCTGA**
 (SEQ ID NO: 297)
 Position 183-**GGCCTGCAGCTGNCTGA**
 (SEQ ID NO: 298)
 Position 184-**GGGCCTGCAGCTNCTGA**
 (SEQ ID NO: 299)
 Position 185-**CGGGCCTGCCAGCNCTGA**

Guide Sequences Only:

55

(SEQ ID NO: 300)
 Position 171-**ACATTTTTGTT**
 (SEQ ID NO: 301) 60
 Position 172-**GACATTTTGT**
 (SEQ ID NO: 302)
 Position 173-**TGACATTTTTG**
 (SEQ ID NO: 303)
 Position 174-**CTGACATTTT**

-Continued

(SEQ ID NO: 304)

Position 175-**GCTGACATTTT**

(SEQ ID NO: 305)

Position 176-**AGCTGACATTTT**

(SEQ ID NO: 306)

Position 177-**CAGCTGACATT**

(SEQ ID NO: 307)

Position 178-**GCAGCTGACATT**

(SEQ ID NO: 308)

Position 179-**TGCAGCTGACAT**

(SEQ ID NO: 309)

Position 180-**CTGCAGCTGACA**

(SEQ ID NO: 310)

Position 181-**CCTGCAGCTGAC**

(SEQ ID NO: 311)

Position 182-**GCCTGCAGCTGA**

(SEQ ID NO: 312)

Position 183-**GGCCTGCAGCTG**

(SEQ ID NO: 313)

Position 184-**GGGCCTGCAGCT**

(SEQ ID NO: 314)

Position 185-**CGGGCCTGCCAGC**

The guide sequences provided above may be used to modify any of the C/D snoRNA sequences to form an engineered snoRNA. The C/D box snoRNA only needs to be modified to position the guide sequence relative to the D box sequence as shown.

As an example of how C/D box snoRNAs may be modified according to the invention, the following nucleic acids encoding engineered snoRNA molecules are shown for illustrative purposes. The D box sequence and guide sequence are underlined. The base complementary to the nucleotide to be modified is shown in bold type.

SNORD73a native sequence (with an AUGA D' box sequence):

(SEQ ID NO: 74)
 AATAAGTGTGAAAAAAAGTTTCGGTCCCAGATGATGCCAGTGATAAC
 AACATTTTCTGATGTT.

SNORD73a sequence engineered for modification of human telomerase at position 176:

(SEQ ID NO: 315)
 AATAAGTGTGAAAAAAAGCTGACATTTGATGATGCCAGTGATAAC
 AACATTTTCTGATGTT.

SNORD73a sequence engineered for modification of human telomerase at position 181:

(SEQ ID NO: 316)
 AATAAGTGTGAAAAAAACCTGCAGCTGACGATGATGCCAGTGATAAC
 CACATTTTCTGATGTT.

SNORD11A native sequence (with a CUGA D' box sequence):

(SEQ ID NO: 120) CAGCCTGAAATGATGACTCTTAAAAAATTCATGTCCTCTGACA

TTTTCTCTGGACACAGTTTGCGCTTATGAATCTGATCAGGCTG.

SNORD11A sequence engineered for modification of human telomerase at position 176:

(SEQ ID NO: 317) CAGCCTGAAATGATGACTCTTAAAAAATTAGCTGACATTTCCTGAC

ATTTTCTCTGGACACAGTTTGCGCTTATGAATCTGATCAGGCTG.

SNORD11A sequence engineered for modification of human telomerase at position 181:

(SEQ ID NO: 318) CAGCCTGAAATGATGACTCTTAAAAAATTCCGCAGCTGACTCTGAC

ATTTTCTCTGGACACAGTTTGCGCTTATGAATCTGATCAGGCTG.

SNORD113-1 native sequence (with a CUGA D' box sequence):

(SEQ ID NO: 123) AAAGTGAGTGATGAATAGTTCTGTGGCATATGAATCATTAATTGATT

AAACCCTAAACTCTGAAGTCC.

SNORD113-1 sequence engineered for modification of human telomerase at position 176:

(SEQ ID NO: 319) AAAGTGAGTGATGAATAGTTCTGTGGCATATGAATCATTAATTGAT

AGCTGACATTTCCTGAAGTCC.

SNORD113-1 sequence engineered for modification of human telomerase at position 181:

(SEQ ID NO: 320) AAAGTGAGTGATGAATAGTTCTGTGGCATATGAATCATTAATTGAT

CCTGCAGCTGACTCTGAAGTCC.

Examples of C/D box snoRNAs include those modified from the yeast snR52 wild type sequence to target specific nucleotides within a pseudoknot of the telomerase RNA, shown below. The base complementary to the nucleotide to be modified is shown in bold type.

Native snR52 sequence (with CTGA D Box sequence):

(SEQ ID NO: 236) TACTATGATGAATGACATTAGCGTGAAC A ATCTCTGATACAAAATCGAA

AGATTTAGGATTAGAAAAAATTATGTTGCCTCCCTCTGAAA.

Guide sequence targeting position 804 of yeast telomerase (TLC1):

(SEQ ID NO: 321) AATAGATT T TTTNCTGA.

Guide sequence targeting position 805 of yeast telomerase (TLC1):

(SEQ ID NO: 322)
GAATAGATT T TTTNCTGA.

Guide sequence targeting position 806 of yeast telomerase (TLC1):

(SEQ ID NO: 323)
TGAATAGA T TTTNCTGA.

Guide sequence targeting position 809 of yeast telomerase (TLC1):

(SEQ ID NO: 324)
CAGTGAAT A GATNCTGA.

Guide sequence targeting position 810 of yeast telomerase (TLC1):

(SEQ ID NO: 325)
TCAGTGAA T AGANCTGA.

Guide sequence targeting position 811 of yeast telomerase (TLC1):

(SEQ ID NO: 326)
TTCAGTGA A TAGNCTGA.

As should be apparent from the above illustrative examples, a guide sequence of an engineered snoRNA is designed to base pair with the target telomerase so that the nucleotide to be modified is complementary to the base 5 bases upstream from the D or D' box of the snoRNA. The guide sequences of the present invention can be used in any engineered snoRNA according to this rule.

It is contemplated that the guide RNA sequences may be longer or shorter than the 12 nucleotide guide sequences illustrated above. The guide sequences may be 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30 or greater nucleotides in length. A person of skill in the art will understand that it is possible to lengthen the guide sequence by adding complementary nucleotides to the 5' end of the guide sequence based on the complementary sequence of the target RNA so that the base to be modified remains base paired with the Box D+5 position. A person of skill in the art will also understand that it is possible to shorten the guide sequence by removing complementary nucleotides from the 5' end of the guide sequence so that the base to be modified remains base paired with the Box D+5 position. It is further contemplated that the guide sequences may have 1, 2, 3, 4, 5, 6, 7, 8 or more mismatched base pairing with the target RNA, depending on the length of the guide sequence.

After an engineered C/D box snoRNA is expressed in a cell, telomerase complexes containing modified telomerase RNA may be recovered from the cell using methods known in the art or using methods as described in the examples below (Qiao, F., et al., *Nat. Struct. Mol. Biol.* 15:634-40 (2008)). It is further contemplated that C/D snoRNA modification of the target telomerase RNA may be effected in vitro by reconstitution of the necessary components of the snoRNA modification machinery, including any snoRNA associated proteins.

Isolated telomerase complexes may be assayed in vitro as is known in the art to determine the effects of modifications.

Examples of telomerase assays may be found in Zappulla, D. C., et al., (*Proc. Natl. Acad. Sci. USA* 101:10024-9 (2004)) and Chen, J. L. and Greider C. W. (*Proc. Natl. Acad. Sci. USA*

102:8080-8085 (2005)). In vitro assays comparing modified telomerase with wild type telomerase activity may be used to determine whether the 2'-O-methylation effected by the engineered snoRNA causes an increase or decrease in telomerase activity.

The in vivo activity of modified telomerase with a modified telomerase RNA may be measured by determining the average length of telomeres in cells containing the engineered snoRNA as compared to the average length of telomeres in cells with unmodified telomerase RNA. Methods for determining telomere length are known in the art, including, e.g., PCR methods, southern blot methods and fluorescent in situ hybridization methods (Allshire R. C. et al., (1989) *Nucleic Acids Res.* 17:4611-4627 (1989); Rufer, N. et al., *Nat. Biotechnol.* 16: 743-747 (1998); Cawthon, R. M., *Nucleic Acids Res.* 30 (10):e47(2002)). The presence of longer telomeres in cells having modified telomerase RNA suggests an increase in telomerase activity from the modification while the presence of shorter telomeres in cells having modified telomerase RNA suggests an decrease in telomerase activity from the modification.

Modified telomere RNA may be isolated from cells using methods known in the art. Primer extension methods known in the art may be used to determine whether or not the targeted position of the telomere RNA was 2'-O-methylated (Ge, J., et al., *Rna* 16:1078-1085 (2010)).

Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention, unless specified.

EXAMPLES

Results

Artificial Box C/D RNA Targeting TLC1 is Efficiently Expressed

Qiao, et al, have recently shown that 2'-OH groups of the triple-helix (A804, A805 and A806) nucleotides and their adjacent nucleotides (U809, A810 and U811) within the conserved pseudoknot structure of TLC1 contribute to telomerase function in vitro ((Qiao, F., et al., *Nat. Struct. Mol. Biol.* 15:634-40 (2008)), (FIG. 1A), thus offering an opportunity for an in vivo functional analysis of these 2'-OH groups using RNA-guided RNA 2'-O-methylation. Six artificial box C/D guide RNAs were designed (gRNA-A804, gRNA-A805, gRNA-A806, gRNA-U809, gRNA-A810, gRNA-U811), each of which targeted one of the six nucleotides in the triple-helix region (FIG. 1A). These artificial guide RNAs were constructed based on snR52, a naturally occurring *S. cerevisiae* box C/D snoRNA that contains two guide sequences, one between box C and box D' and the other between box C' and box D (FIG. 1B). The short guide sequence between box C and box D' or between box C' and box D was altered to target the TLC1 nucleotides; all other nucleotide sequences of snR52 were left unchanged. The artificial box C/D RNA genes were separately inserted into a 2 μ vector, with the expression of the box C/D guide RNAs under the control of the GPD promoter.

Upon transformation, the expression of guide RNA was measured using northern analysis. Northern results showed that every guide RNA was efficiently expressed (FIG. 2A, lanes 3-8).

Artificial Box C/D Guide RNA is Functionally Active In Vivo

To ensure that the artificial box C/D guide RNA had a sufficient level of activity, a primer extension-based 2'-O-methylation assay to detect 2'-O-methylation of TLC1 at the

target sites was carried out. It is well established that at low dNTP concentrations, primer extension will stop/pause precisely one nucleotide before the 2'-O-methylated site (Maden, B. E., et al., *Biochimie* 77:22-9 (1995)). When a 5 guide RNA was expressed, a stop/pause signal corresponding to its target site was clearly detected under low-dNTP conditions (FIG. 2B, lanes 4, 6, 8, 10, 12 and 14). As expected, when high dNTP concentrations were used, the stop/pause signal was barely detected (FIG. 2B, lanes 3, 5, 7, 9, 11 and 13). Thus, these results demonstrated that each guide RNA was capable of guiding TLC1 2'-O-methylation at its target site.

Given that 2'-O-methylation efficiency is important for determining the degree to which the modification influences telomerase activity, the level of 2'-O-methylation at each target site was further quantified. A recently developed ligation based assay was used, in which a pair of DNA primers are aligned with the RNA substrate upon hybridization, leaving the ligation junction (nick) 5' or 3' of the test nucleotide in the RNA substrate (Saikia, M., et al., *Rna* 12:2025-33 (2006)) (FIG. 2C). If the test nucleotide is 2'-O-methylated, the two primers will not be ligated if the ligation junction is placed 3' of the modified nucleotide (discriminating or D primer pair), 15 but they will be quantitatively ligated if the junction is placed 5' of the modified nucleotide (non-discriminating or ND primer pair). If the test nucleotide is not 2'-O-methylated, the two primers (either D or ND primer pair) will be quantitatively ligated regardless of where the junction is (FIG. 2C). 20 The ligation efficiency should correlate well with the modification level at the test site. Comparison of the ligation ratios will thus allow quantification of 2'-O-methylation at the test nucleotide.

FIGS. 2D and 2E show the ligation experiments using 25 TLC1 RNA harvested after 30 and 590 generations, respectively. When the ND primer pair was used, ligation efficiency (the ratio of the ligated product to the loading control) was about the same for all TLC1 RNAs at all sites tested, including untargeted TLC1 RNA (con.) and gRNA targeted TLC1 40 RNA (FIGS. 2D and 2E, compare even-numbered lanes). However, when the D primer pair was used, a drastic reduction in ligation was observed in reactions where TLC1 RNA was isolated from cells expressing gRNAs (FIGS. 2D and 2E, compare lanes 3, 7, 11, 15, 19 and 23 with other odd-numbered lanes). These results indicated a high level (70-90%) of 45 2'-O-methylation at all target sites regardless of the number of cell generations (30 or 590 generations) (compare FIG. 2D with FIG. 2E, and compare targeted lanes with untargeted control lanes). These results also indicated that 2'-Omethylation was target specific, as reduced ligation was detected only in reactions where a target-specific gRNA was expressed and a D primer pair for the respective target site was used (FIG. 2D, FIG. 2E, and data not shown).

2'-O-Methylation in the Triple-Helix Region does not Change 50 TLC1 RNA Levels

Whether 2'-O-methylation in the triple-helix region would affect TLC1 RNA levels was then tested. Using northern analysis, the levels of TLC1 RNA in wild-type control cells and in cells expressing various artificial gRNAs were 55 assessed. Total RNAs were isolated from these cells after different numbers of generations, and northern analysis was carried out using a TLC1-specific probe and a U1-specific probe as an internal control. The signals of TLC1 RNA relative to U1 RNA were virtually identical in all the cells after 60, 310 and 590 generations (FIG. 3A), indicating that targeted 2'-Omethylation had no effect on steady-state levels of 65 TLC1 RNA.

2'-O-Methylated TLC1 RNA is Assembled into Telomerase RNP

To determine whether 2'-O-methylated TLC1 RNA was incorporated into telomerase RNP, a glycerol gradient analysis was carried out. TLC1 RNA from either the control strain or the strain expressing gRNA-U809 peaked in the same fractions, just as U1 snRNP did in both strains (FIG. 3B). The RNA from the telomerase RNP peaks was then isolated and the 2'-O-methylation assay was performed. Although no 2'-O-methylation signal was observed in control TLC1, RNA (FIG. 3C; lanes 1 and 2), a clear 2'-Omethylation signal corresponding to U809 was detected in TLC1 RNA isolated from cells expressing gRNA-U809 (lanes 3 and 4). Thus, 2'-O-methylated TLC1 RNA appeared to be incorporated into the telomerase RNP.

To further confirm these gradient results, an independent approach was performed, namely Est2p-co-precipitation assay. A strain in which the telomerase reverse transcriptase gene EST2 is fused with a protein A tag (Friedman, K. L., et al., *Genes Dev.* 13:2863-74 (1999)) was used in this approach.

Upon transformation with the plasmid containing an artificial box C/D RNA gene, cells were harvested, and Est2p was pulled down through protein A-IgG precipitation. Western blotting was used to measure the precipitated Est2p. As shown in FIG. 3D, a nearly identical amount of Est2p was precipitated [compare the intensity of the Est2 band in lanes 1-8 (Est2-tagged lanes)]. As a control, when untagged strain was used, an Est2p was detected (lane 9). RNA co-precipitated with Est2p was also recovered and analyzed. Northern blotting indicated that TLC1 RNA was efficiently co-precipitated with Est2p regardless of whether cells were transformed with a plasmid containing no gRNA gene (lane 8), a random box C/D RNA gene (lane 1; control) or any one of the six artificial box C/D RNA genes (lanes 2-7). 2'-O-methylation was further assayed, and these experiments showed that Est2p-associated TLC1 RNA, isolated from cells expressing a gRNA, was efficiently 2'-O-methylated at the expected target site (FIG. 3E). Thus, it appears that 2'-O-methylated TLC1 RNA is efficiently incorporated into telomerase RNP (at least associated with Est2p).

In Vitro Functional Assay Indicates that 2'-O-Methylation at U809 (Adjacent to the Triple-Helix) Reduces Telomerase Activity

To assess whether 2'-O-methylation at the nucleotides in and near the triple-helix structure affects function, the in vitro telomerase activity assay was carried out (Friedman, K. L., et al., *Genes Dev.* 13:2863-74 (1999)) using the Est2p-bound fractions described above. As shown in FIG. 4, targeted 2'-Omethylation at position U809 resulted in a substantial reduction of telomerase activity (FIG. 4A, lanes 9 and 10; FIG. 4B). When A804 or A805 was targeted by the artificial gRNAs, a relatively small but statistically significant enhancement of telomerase activity was observed (FIG. 4A, compare lanes 3-6 with lanes 1 and 2; FIG. 4B). 2'-O-methylation at the other sites had no significant effect on telomerase activity (FIGS. 4A and 4B).

A804 and A805 are in the triple-helix structure, and U809 is in a nearby stem adjacent to the triple-helix (FIG. 1A). The fact that 2'-O-methylation at U809 reduced telomerase activity is consistent with the previous in vitro study by Qiao, et al., who showed that combined substitution of the 2'-OH groups of all three adjacent nucleotides (U809, A810 and U811) with 2'-H groups resulted in diminished telomerase activity. In contrast, targeted 2'-O-methylation directed at the triple-helix nucleotide A804 or A805 resulted in no reduction of telomerase activity; rather, a slight increase in telomerase activity was observed. This observation is different from that made by

Qiao, et al., who show a substantial reduction of telomerase activity when the 2'-OH groups of all three triple-helix nucleotides are simultaneously changed to 2'-H groups.

This apparent inconsistency may be due to the fact that the 2'-OH groups were changed to 2'-O-methyl groups whereas in the previous study, the 2'-OH groups were changed them to 2'-H groups.

A804, A805 and U809 in the Triple-Helix Region are Key 2'-O-methylation Targets for Influencing Telomerase Activity In Vivo

The effect of the six artificial guide RNAs on chromosome end maintenance in vivo was then assessed. Using Southern blotting, telomere length in cells expressing these artificial gRNAs was monitored. As shown in FIG. 5, when gRNA-U809 was expressed, chromosome ends progressively shortened with time [compare lanes 29 and 30 (590 generations) with lanes 27 and 28 (310 generations) and with lanes 25 and 26 (30 generations) or lanes 31 and 32 (30 generations)]. Interestingly, the chromosome ends moderately lengthened when gRNA-A804 or gRNA-A805 was expressed (compare lanes 11 and 12 with lanes 9 and 10, and lanes 7 and 8; also compare lanes 17 and 18 with lanes 15 and 16, and lanes 13 and 14). In contrast, no apparent changes in telomere length were detected in cells expressing any other gRNAs (lanes 19-24 and 33-44) or no gRNA (data not shown). These results are consistent with the in vitro assay results described above (also see Discussion below), pinpointing three critical nucleotides: A804 and A805 for lengthening and U809 for shortening. The other sites appeared to be less important for telomerase activity when targeted individually.

Targeted 2'-O-Methylation Influences Telomerase Activity as Shown by the Telomere Position Effect Assay

To further prove the effectiveness of the in vivo approach, an independent phenotypic assay involving the yeast strain (yHK53 rad52Δ::KanMX)(37) was used in which URA3 is inserted into chromosome VII near its end. Under normal conditions, the chromosome ends are stable and URA3 is silenced by the telomere position effect (Gottschling, D. E., et al., *Cell* 63:751-62 (1990)), thus allowing cells to grow on 5-FOA medium. When the chromosome ends are progressively shortened, URA3 is, however, progressively activated, which results in cell death on 5-FOA containing medium. Using this assay, a clear progressive growth defect for cells expressing gRNA-U809 was observed. In contrast, no growth defect on 5-FOA medium was observed when cells were transformed with any other gRNAs targeting a single nucleotide in the triple-helix region or with a control box C/D guide RNA containing a random guide sequence (FIG. 6A).

To confirm this observation, the telomere length of chromosome VII was measured using Southern analysis. Whereas no change in telomere length was detected when cells expressed a random (control) gRNA (FIG. 6B; compare lane 1 with lane 2), substantial telomere shortening was observed when cells were transformed with gRNAU809 (compare lane 3 with lane 4). Interestingly, a moderate lengthening of the end of chromosome VII was observed when cells received gRNA-A804 (compare lane 5 with lane 6), which is consistent with what was observed in other experiments (see FIGS. 4 and 5). Taken together, these results indicate that targeted telomerase RNA 2'-O-methylation is a very effective strategy for blocking telomerase activity in vivo.

Discussion

Using RNA-guided RNA modification, 2'-O-methylation sites were introduced into specific nucleotides in or adjacent to the triple-helix structure of *S. cerevisiae* TLC1 RNA, thereby affecting telomerase activity in vivo. Specifically, 2'-O-methylation at U809 resulted in telomere shortening,

whereas 2'-O-methylation at A804 and A805 led to moderate lengthening of telomeres. These results appear to be consistent with the notion that the 2'-OH groups of the nucleotides within the triple-helix and the nearby stem contribute to function (directly or indirectly) (Qiao, F., et al., *Nat. Struct. Mol. Biol.* 15:634-40 (2008)). These results also suggest that RNA-guided RNA modification can serve as an effective tool for regulating telomerase activity (and RNA function in general) in vivo. With respect to telomerase function, Qiao, et al. demonstrated, using an in vitro system, that the 2'-OH groups of nucleotides in the triple-helix region, which are proximal to the catalytic active site, contribute to telomerase activity in vitro (Qiao, F., et al., *Nat. Struct. Mol. Biol.* 15:634-40 (2008)). Specifically, they show that the simultaneous changing of the 2'-OH groups of the triple-helix nucleotides (A804, A805, and A806) to 2'-H groups results in a substantial reduction in telomerase activity.

When the nucleotides (U809, A810 and U811) adjacent to the triple-helix structure are simultaneously changed to 2'-deoxy nucleotides, a substantial reduction of in vitro telomerase activity was observed. The above results show a clear reduction of telomerase activity both in vitro (FIG. 4) and in vivo (FIGS. 5 and 6) when U809, one of the three nucleotides adjacent to the triple-helix structure, was targeted for 2'-O-methylation, although targeting of either A810 or U811 did not lead to the reduction of telomerase activity. The above results thus suggest that it is the 2'-OH group of U809, rather than the 2'-OH groups of A810 and U811, that contributes to function. This approach added a methyl group to the sugar ring, thus the possibility cannot be excluded that such a modification disrupted the local structure of the RNA, thereby resulting in the reduction of telomerase activity.

Rather surprisingly, telomere lengthening was detected when 2'-O-methylation was introduced into either A804 or A805, two of the three triple-helix nucleotides (FIG. 5). This enhancing effect is in contrast to the inhibitory effect previously observed when the 2'-OH groups of the triple-helix nucleotides were changed to 2'-H groups (Qiao, F., et al., *Nat. Struct. Mol. Biol.* 15:634-40 (2008)). It is conceivable that if the 2'-OH group of A804 and/or A805 contributes directly to catalysis (as U809 does), changing the 2'-OH group to either 2'-H or 2'-OMethyl should dramatically alter its chemical properties (e.g., preventing hydrogen bond donation), thus resulting in a reduction (rather than an enhancement) of telomerase activity. Without wishing to be bound by theory, one possible explanation is that the 2'-OH groups of the triple-helix nucleotides may indirectly contribute to function (or catalysis): modifications at the 2' position may influence the configuration of the sugar pucker, either C3'-endo or C2'-endo configuration, which may in turn affect its function. A sugar pucker with a 2'-OH favors the C3'-endo conformation when compared with a sugar pucker with a 2'-H. However, when the 2'-OH of the sugar pucker is methylated (2'-OMethyl), the C3'-endo conformation becomes even more favorable (Hou, Y. M., et al., *Nucleic Acids Res.* 29:976-85 (2001); Uesugi, S., et al., *Tetrahedron Letters* 20:4073 (1979)). This order of preference (2'-OMethyl>2'-OH>2'-H) for the C3'-endo conformation would be consistent with the observed effect of different 2' moieties on telomerase activity if the C3'-endo (rather than C2'-endo) is the more functionally favorable conformation. Specifically, relative to 2'-OH, 2'-OMethyl enhances, while 2'-H inhibits, telomerase activity.

It is possible that it is the extensive base-pairing interactions between the guide sequence of gRNA and the target sequence of TLC RNA, rather than 2'-O-methylation per se, that has influenced telomerase activity. For instance, the base-

pairing may have altered TLC RNA folding, localization and even telomerase RNP assembly. However, this possibility is unlikely for at least two reasons. First, clean and specific 2'-O-methylation at target sites was detected (FIG. 2B and FIG. 3E). Second, not all gRNAs, which targeted different nucleotides in the same region, exhibited an inhibitory or enhancing effect on telomerase activity. For instance, gRNA-U809 and gRNA-A810 targeted nucleotides adjacent to each other, but only gRNA-U809 exhibited an inhibitory effect on telomerase activity. Because both gRNAs maintained almost identical complementarity with TLC1 RNA, these results suggest that the observed inhibitory effect of targeting U809 was truly 2'-O-methylation-specific rather than an antisense effect that could impact TLC1 RNA folding, localization or RNP assembly.

Likewise, the same reasoning can be used to explain the enhancing effect of targeting A804 or A805 (comparing gRNA-A804 or gRNA-A805 with gRNA-A806). It should also be noted that the artificial guide RNAs used in this study may have unintended target(s), thus raising concerns about substrate specificity. To address this issue, the guide sequences (12 nt) were used to conduct a BLAST search against the yeast genome, with an attempt to identify other potential target RNAs. This search generated only few such candidates: Six (STE24, PRM4, NAM7, SMI1, PUF3 and TUS1) for gRNA-A804 and gRNA-A805, and one (STB4) for U809. None of these potential targets have known functions in telomere maintenance. Thus, it is unlikely that the observed effects are due to the non-specific effect of modifications of unintended off-targets.

With regard to the application of RNA-guided RNA modification, it is shown herein that an artificial box C/D guide RNA can efficiently target TLC1 2'-O-methylation at specific sites. The artificial guide RNA can be constructed according to a naturally occurring box C/D snoRNA (e.g., snR52). According to the sequence/site to be targeted, only the short guide sequences of the original box C/D snoRNA need to be altered, and the remaining sequences do not have to be changed. Such an approach to target an RNA at a specific site appears to be straightforward and effective and should be applicable to many different RNA types.

Although any nucleotides of an RNA can, in theory, be targeted in vivo, control of RNA localization remains a major issue that must be addressed. It is known that box C/D snoRNA (or RNP) is localized to the nucleoli and/or Cajal bodies (Kiss, T. et al., *Embo J* 20:3617-22 (2001)); however, some potential target RNAs (for example, mRNA) do not co-localize with snoRNA. The distinct localization of RNAs raises the question of whether all nuclear RNAs (including those that are temporarily present in the nucleus) can be targeted for modification. Although localization studies detect snoRNAs in the nucleoli and/or Cajal bodies (Balakin, et al., *Cell* 86:823-34 (1996), Darzacq, X., et al., *Embo J* 21:2746-56 (2002)), such studies do not exclude the possibility that snoRNAs may exist in the nucleoplasm as well. Perhaps the failure to detect snoRNAs in the nucleoplasm merely reflects the fact that snoRNAs are too dilute to be detected in this subnuclear compartment. In this regard, two reports have suggested that a U2-specific guide RNA (Zhao, X., et al., *Rna* 8:1515-25 (2002)) and a guide RNA specific for spliced-leader RNA (a special type of spliceosomal snRNA involved in trans-splicing) (Liang, X. H., et al., *Rna* 8:237-46 (2002)) may both reside within the nucleoplasm rather than within the nucleolus or Cajal bodies. Such conclusions are bolstered by a recent finding that suggests the presence of a number of *Drosophila melanogaster* snRNA-specific guide RNAs in the nucleoplasm as well as in Cajal bodies (Deryusheva, S., et al.,

Mol. Biol. Cell 20(24):5250-9 (2009)). In this regard, the present inventors and others have shown that mRNA as well as pre-mRNA can be targeted by artificial guide RNAs for modification in vivo (Cavaillé, J., M. et al., *Nature* 383:732-5 (1996); Zhao, X., et al., *Nat. Methods* 5:95-100 (2008)); (Karijolich and Yu, unpublished data). Thus, it appears that RNA-guided RNA modification can occur in one or a few different nuclear subcompartments, including the nucleolus, Cajal bodies and/or even the nucleoplasm, and that RNA-guided RNA modification is a highly useful approach for regulating RNA function in eukaryotic cells.

Methods

Plasmids and *S. cerevisiae* Strains

pSEC (snoRNA expression cassette) was constructed based on the parental yEPlac181 (a 2 μ LEU2 vector kindly provided by Dr. E. M. Phizicky at University of Rochester) (Culver, G. M., et al., *J Biol. Chem.* 272:13203-10 (1997)). The GPD promoter region (a sequence corresponding to nucleotides -655 to 0 of TDH3) was inserted between EcoRI and BamH1. A 65-nt RNT1 element sequence (5'-TTTT-TATTTCTTCTAAAGTGGGTACTGGCAG-GAGTCGGGGCCTAGTTAGAGA GAAGTAGACTCA-3') (SEQ ID NO: 327), corresponding to part of 35S pre-rRNA 3' ETS that is recognized by endonuclease RNT1 (RNase III activity) (Fatica, A., et al., *Embo J* 19:6218-29 (2000)), was inserted between BamH1 and Sall; a 55-nt snR13 termination sequence (5'-AGTAATCCITCTTACAT-TGTATCGTAGCGCTGCATATATAATGCGTAAAATTTC-3') (SEQ ID NO: 328), corresponding to nucleotides 26 to 80 downstream of snR13, was inserted between PstI and HindIII. The pSEC cassette thus constructed contains a pair of restriction sites (Sall and PstI) flanked by the RNT1 element on the 5' side and the snR13 termination sequence on the 3' side (Fatica, A., et al., *Embo J* 19:6218-29 (2000)). These two restriction sites were then used for insertion of an snR52-based artificial box C/D RNA gene (in which one of the guide sequences was altered), resulting in the production of pSEC-gRNA-A804, pSEC-gRNA-A805, pSECgRNA-A806, pSEC-gRNA-U809, pSEC-gRNA-A810, pSEC-gRNA-U811. Upon transformation into yeast cells, the mature artificial box C/D RNA (gRNA) was efficiently expressed (FIG. 2A).

Strain yCH-001 (snR52Δ::URA3, BY4741 background) was used for analyzing the expression of snR52-based artificial gRNAs. In addition, using the KanMX4 cassette (Ma, X., et al., *Embo J* 24:2403-13 (2005)), deleted RAD52 was deleted from another haploid strain yHK53 (Yu, Q., et al., *J. Biol. Chem.* 284:740-50 (2009)) (BY4741 background; MATa his3Δ1 leu2Δ0 met15Δ0 ura3Δ0 TelVII-URA3; kindly provided by Dr. X. Bi at the University of Rochester), generating a new strain (yCH-002) that no longer had the Rad52-mediated alternative telomere maintenance pathway. yCH-002 was then used for both the telomere length assay (see below) and the telomere position effect assay (see below).

A yeast strain YKF103 (kindly provided by the Cech group), in which the chromosomal EST2 gene is fused with a protein A tag, was used for IgG Immunoprecipitation assay (Friedman, K. L., et al., *Genes Dev.* 13:2863-74 (1999)) (see below).

Northern Blot Assay

To examine gRNA expression, total RNAs isolated from cells (yCH-001) expressing no gRNA, a control gRNA, gRNA-A804, gRNA-A805, gRNA-A806, gRNA-U809, gRNA-A810, or gRNA-U811 were used for Northern blot analysis (FIG. 2A). The hybridization was performed using two 5' end—radiolabeled DNA oligos: the first one was complementary to a snR52 sequence between box C' and box

D' (5'-GTTTTCTAACCTAAAATCTTCGATTT-3') (SEQ ID NO: 329), and the second one was complementary to U1 snRNA (5'-AACGTCCTTCTACTATTGGAA-3') (SEQ ID NO: 330).

To check whether 2'-O-methylation affects TLC1 levels, yeast strain yCH-002 was transformed with pSEC-gRNA-Control, pSEC-gRNA-A804, pSEC-gRNA-A805, pSECgRNA-A806, pSEC-gRNA-U809, pSEC-gRNA-A810, or pSEC-gRNA-U811. After 30, 310, or 590 generations, cells were collected, total RNAs isolated, and Northern blotting performed. In brief, upon electrophoresis on a 4% polyacrylamide/8 M urea gel, RNAs were transferred to a HYBOND-N+ membrane (Amersham Pharmacia), and hybridized at room temperature with two 5' end-labeled DNA oligo probes; one was complementary to TLC1 RNA (5'-TTCTCTGTCACATCGITCGATGTAC-3') (SEQ ID NO: 331), and the other was complementary to U1 snRNA (5'-AACGTCCTTCTACTATTGGAA-3') (SEQ ID NO: 332). After an overnight hybridization, the membrane was extensively washed, and TLC1 and U1 signals were revealed by autoradiography.

Northern analysis was also carried out to check whether 2'-O-methylated TLC1 RNA associated with Est2p (or was assembled onto RNP) (see Co-immunoprecipitation and Glycerol gradient assay below),
Primer Extension-Based 2'-O-Methylation Assay

A standard primer extension-based modification assay (with high and low dNTP concentrations) was performed essentially as described (42) to detect RNA 2'-O-methylation. Briefly, ~6 μ g of total RNA, or ~200 ng of Co-immunoprecipitated TLC1 RNA (see below), was mixed with 5'-radio-labeled DNA oligonucleotide Detect-TLC-2OMe (5'-TTCTCTGTCACATCGITCGATGTAC-3') (SEQ ID NO 333), and the primer extension reaction was carried out in the presence of either 1 mM dNTPs (high) or 0.01 mM dNTPs (low).

The reactions were incubated at 42° C. for 30 min and resolved on an 8% polyacryamide/8 M urea gel.

Ligation-Based Quantitative 2'-O-Methylation Assay

Using biotinylated antisense TLC1 DNA oligonucleotide (5'-biotin-TCAATCCGAAATCCGACACTATCTC-3') (SEQ ID NO: 334) and biotin-streptavidin affinity chromatography (Zhao, X., et al., *Rna* 8:1515-25 (2002), Zhao, X., et al., *Rna* 10:681-90 (2004)), TLC1 RNA was purified from 1 L yeast cells (OD600=7.0) that expressed no gRNA, a random (control) gRNA or gRNA targeting the nucleotides in and adjacent to the triple-helix region. Purified cellular TLC1 RNA served as the template in the subsequent ligation reaction.

To quantify the 2'-O-methylation at any particular site of TLC1 RNA, two parallel ligation reactions (discriminating and non-discriminating reactions) with two different site specific pairs of oligodeoxynucleotides were carried out at 37° C. for 30 min in the presence of 66 mM Tris-HCl (pH 7.6), 6.6 mM MgCl₂, 10 mM dithiothreitol, 66 mM ATP, 15% DMSO, 0.125 U/ μ L T4 DNA ligase (Saikia, M., et al., *Rna* 12:2025-33 (2006)).

In the discriminating ligation reaction, a pair of discriminating DNA oligonucleotides (D oligo pair) was used to hybridize with TLC1 RNA. Consequently, the two oligos were precisely aligned, placing a nick or the ligation junction (between the two oligos) on the 3' side of U809. In the non-discriminating ligation reaction, a pair of nondiscriminating DNA oligonucleotides (ND oligo pair) was used. Upon hybridization with TLC1 RNA, the oligos were aligned, leaving a nick or the ligation junction on the 5' side of U809. It is well established that if the target nucleotide (U809) is 2'-O-

methylated, only the non-discriminating oligo pair will be ligated; however, if U809 is not 2'-O-methylated, both pairs of oligos will be ligated (Saikia, M., et al., *Rna* 12:2025-33 (2006)), thus providing a quantitative measurement of 2'-O-methylation at U809.

For position 804 (A804), the D oligo pair were DF-804, 5'-GAAATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 335), and DA-804, 5'-[32P]TTTTTATTTCAGTTAGTGGG-3' (SEQ ID NO: 336); the ND oligo pair were NF-804, 5'-GAAATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 337), and NA-804, 5'-[32P]TTTTTATTTCAGTTAGTGGG-3' (SEQ ID NO: 338). Similarly, for positions 805, 806, 809, 810 and 811, the D oligo pairs were, respectively, DF-805, 5'-GGAAATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 339), and DA-805, 5'-[32P]TTTTTATTTCAGTTAGTGGG-3' (SEQ ID NO: 340), DF-806, 5'-TGGAAATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 341), and DA-806, 5'-[32P]TTTTTATTTCAGTTAGTGGG-3' (SEQ ID NO: 342), DF-809, 5'-AATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 343), and DA-809, 5'-[32P]AGATTTCATCAGTTAGTGGG-3' (SEQ ID NO: 344), DF-810, 5'-AAATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 345), and DA-810, 5'-[32P]TAGATTTCAGTTAGTGGG-3' (SEQ ID NO: 346), and DF-811, 5'-GAAATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 347), and DA-811, 5'-[32P]AGATTTCATCAGTTAGTGGG-3' (SEQ ID NO: 348); the ND oligo pairs were, respectively, NF-805, 5'-GGAAATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 349), and NA-805, 5'-[32P]TTTTTATTTCAGTTAGTGGG-3' (SEQ ID NO: 350), NF-806, 5'-TGGAAATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 351), and NA-806, 5'-[32P]TTTTTATTTCAGTTAGTGGG-3' (SEQ ID NO: 352), NF-809, 5'-AATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 353), and NA-809, 5'-[32P]GATTTCATCAGTTAGTGGG-3' (SEQ ID NO: 354), NF-810, 5'-AAATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 355), and NA-810, 5'-[32P]AGATTTCATCAGTTAGTGGG-3' (SEQ ID NO: 356), and NF-811, 5'-GAAATTTCATCAGTAAGTTCACTGAATAGATT-3' (SEQ ID NO: 357), and NA-811, 5'-[32P]TAGATTTCAGTTAGTGGG-3' (SEQ ID NO: 358). For sites U809, A810, and U811, the ligation products were 50 nucleotides long, and for sites A804, A805, and A806, the ligation products were 57 nucleotides long.

In all ligation reactions, another pair of DNA oligonucleotides (NF-1145, 5'-TTCCAAAAATTATCTAAA-3' (SEQ ID NO: 359); NA-1145, 5'-[321]TGCATCGAAGGCATT-AGGAGAAGTA-3') (SEQ ID NO: 360), which placed the ligation junction 5' of U1145 (a non-targeting site) of TLC1 RNA, was used as a loading control.

After the ligation reaction, the radioactively labeled oligos (ligated and unligated) were resolved on an 8% polyacrylamide/8 M urea gel and quantified using a PhosphorImager (Molecular Dynamics).

Glycerol Gradient Assay

The procedure was essentially as described (Lingner, J., et al., *Science* 276:561-7 (1997)). Briefly, yeast cells from 2 L overnight cultures (SD leucine drop-out medium) were harvested at OD₆₀₀=1.0. Pelleted cells were suspended in 4 mL of extraction buffer (20 mM Tris-acetate (pH 7.5), 300 mM potassium glutamate, 1.1 mM MgCl₂, 0.1 mM EDTA, 5% glycerol, 1 mM dithiothreitol and 0.5 mM phenylmethylsulfonyl fluoride), placed in liquid nitrogen and ground with a mortar and pestle for 30 min. The lysate was concentrated three-fold in a Vivaspin ultrafiltration spin column and then

loaded on the top of a 15-40% continuous glycerol gradient prepared with the extraction buffer. Ultracentrifugation (SW41Ti rotor, 150,000×g) was performed at 4° C. for 18 h. Nineteen fractions were collected, and RNA was extracted from each fraction for northern analysis (see above).

Co-Immunoprecipitation

Extracts were prepared from yeast cells (strain YKF103) expressing a control gRNA, gRNA-A804, gRNA-A805, gRNA-A806, gRNA-U809, gRNA-A810 or gRNAU811, according to the glass-bead lysis method (Friedman, K. L., et al., *Genes Dev.* 13:2863-74 (1999)). Briefly, 500 mL yeast cells (OD₆₀₀=1.0) were lysed, by glass-bead beating, in TMG-300 NaCl buffer containing 10 mM Tris-HCl, pH 8.0, 1 mM MgCl₂, 10% glycerol, 0.1 mM DTT, and 300 mM NaCl. After clarification by brief centrifugation (15,000×g at 4° C. for 5 min, repeated 3 times), total protein concentration was adjusted to 5 mg/mL. Upon addition of Tween-20 (to a final concentration of 0.5%), 500 μL of extract was mixed with 10 μL IgG Sepharose 6 Fast flow beads (GE healthcare). After overnight nutation at 4° C., the beads were collected, washed 3 times with TMG-200 NaCl-Tween buffer (10 mM Tris-HCl, pH 8.0, 1 mM MgCl₂, 10% glycerol, 0.1 mM DTT, 200 mM NaCl, and 0.5 Tween) and one time with TMG-50 NaCl buffer (10 mM Tris-HCl, pH 8.0, 1 mM MgCl₂, 10% glycerol, 0.1 mM DTT, 50 mM NaCl), and then resuspended in 20 μL TMG-50 NaCl buffer with 0.5 mM DTT. The beads were split into two equal aliquots of 10 μL each. One aliquot was used for *in vitro* telomerase activity assay (see below), and the other for TLC1 RNA extraction and analysis.

For TLC1 RNA extraction, 10 μL beads were treated with proteinase K at 37° C. for 30 min in a 200 μL reaction (10 mM Tris-HCl pH 8.0, 0.5% SDS, 0.4 mg/ml proteinase K). RNA was then PCA extracted and ethanol precipitated. Recovered TLC1 RNA was subsequently subjected to primer extension analysis (2'-O-methylation assay) and Northern blot analysis (see above).

Western Blot Assay

Western blot was performed essentially as previously described (Seto, A. G., et al., *Rna* 9:1323-32 (2003)). Briefly, 10 μL of immunoprecipitated beads were mixed with 10 μL 2× Laemmli loading buffer (125 mM Tris-HCl, pH 6.8, 4% SDS, 50% glycerol, 5% β-mercaptoethanol, 0.02% bromophenol blue). Upon incubation at 95° C. for 5 min, the supernatant was resolved on a 4-15% Tris-glycine gel (Bio-Rad). Protein was then transferred to a Protran nitrocellulose membrane (Whatman) and probed with antibodies. The primary antibody was rabbit IgG (Sigma), and the secondary was goat anti-rabbit IgG-AP conjugated antibody (BioRad). Telomerase Activity Assay

In vitro telomerase activity assay was carried out as previously described (Seto, A. G., et al., *Rna* 9:1323-32 (2003)). Briefly, 2 μL of Est2p-bound beads derived from immunoprecipitation (see above) were added to a final 10 μL of reaction containing 40 mM Tris-HCl, pH 8.0, 50 mM NaCl, 5% glycerol, 2.5 mM MgCl₂, 0.5 mM spermidine, 0.5 mM DTT, 2.5 μM telomerase substrate (5'-TGTGGTGTGTGGG-3') (SEQ ID NO: 361), 1 μL [α-32P] dGTP (10 μCi/μL), 1 μL [α-32P] dTTP (10 μCi/μL). After incubation at 30° C. for 20 min, the reaction was terminated by addition of 200 μL of proteinase K buffer (10 mM Tris-HCl pH 8.0, 0.5 SDS) and 4 μL of proteinase K (20 mg/mL). The mixture was then incubated at 60° C. for 30 min. Nucleic acids were recovered by PCA extraction and ethanol precipitation. The primer-extended DNA products were resolved on a 14% polyacrylamide denaturing gel, and visualized by autoradiography.

29

Southern Analysis to Measure Telomere Length

For Southern blotting, yeast cells were grown to saturation in 20 mL SD leucine drop-out medium. The genomic DNA was subsequently extracted. Briefly, yeast cells were suspended in extraction buffer (10 mM Tris-HCl pH 8.0, 2% Triton X-100, 1% SDS, 1 mM EDTA). Upon the addition of saturated phenol and glass beads, cells were broken by vigorous vortexing. Cell extracts were treated with proteinase K (~0.4 mg/mL) at 55° C. for 2 h, and genomic DNA was subsequently purified via PureLink genomic DNA spin columns (Invitrogen). The purified genomic DNA was digested with XbaI, resolved on a 0.8% agarose gel, transferred onto a HYBOND-N+ membrane (Amersham Pharmacia) and hybridized with two radiolabeled probes, one against the telomeric repeat sequence probe (5'-TGTGGGTGTTG-3') (SEQ ID NO: 362) and the other (as a control) against chromosome IV (nucleotides 31051-31075; 5'-GTCTGGCCTATGGTGCAGTAGTAC-3') (SEQ ID NO: 363).

For detecting URA3 integrated into chromosome VII (yCH-002 strain), purified genomic DNA was digested with

30

PstI and hybridized with a URA3-specific probe (5'-ACATTATTGTTGAAAGAGGACT-3') (SEQ ID NO: 364) and a control probe against chromosome IV (nucleotides 194700-194676; 5'-GATACACCTCCGTTCTGACCCAT-3') (SEQ ID NO: 365).

Telomere Position Effect Assay

After transformation with various pSEC-gRNA plasmids, cells were plated onto solid medium, and a single colony was 10 picked and grown to saturation in 5 mL of SD leucine drop-out medium. One microliter of the liquid culture was then withdrawn, placed in 5 mL of fresh SD leucine drop-out medium and grown to saturation again. This cycle was 15 repeated until the cells reached 590 generations. At 310, 450 and 590 generations, an aliquot of cells was saved and stored at -80° C. for future use. To assay growth phenotype, cells from different generations were first diluted to OD₆₀₀=0.1 and then plated with a series of five-fold dilutions on the SD leucine drop-out solid medium with or without 5-FOA (1 mg/mL). The growth phenotype was monitored at 30° C.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 433

<210> SEQ ID NO 1
<211> LENGTH: 91
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

tcactgtat gatggtttcc caacattcgc agtttccacc agaaaaggttt tccttagtgt	60
tggtaaaccc ttcccttgat gtctgagtga g	91

<210> SEQ ID NO 2
<211> LENGTH: 92
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

tcactatgtat gattgggttgc cagacattcg cagtttccac cagaaatgtt tttcctttag	60
ttggccagtt ctcccttggta tgtctgagtg ag	92

<210> SEQ ID NO 3
<211> LENGTH: 148
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

ttcgtatgaa gagatgtatcg cgagtctgac ttggggatgt tcttttgc caggtggact	60
actctgtgtgc gcgttctgtg gcacagttta aagagccctg gttgaagtaa tttcctaaag	120
atgacttaga ggcattttgtc tgagaagg	148

<210> SEQ ID NO 4
<211> LENGTH: 146
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

tttcgtatgat gacacgtatcg cgagtcagaa aggtcacgtc ctgtcttgg tccttgcag	60
tgccatgttc tgtggtgctg tgcacgagg ccttggcag aagtgtccca tttatgtatc	120
gattnagagg cattttgtctg agaagg	146

-continued

-continued

```

<211> LENGTH: 84
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11
tttgggtga aatatgatga gtgtacaaaa tcttgattta agtgaatgaa aaattacaag      60
atccaaactct gatttcagcc agag                                         84

<210> SEQ ID NO 12
<211> LENGTH: 80
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12
tggatatgtatgactgattac ctgagaaaata attgatgaaa tctcaagaaa attcctctag      60
atagtcaagt tctgatccag                                         80

<210> SEQ ID NO 13
<211> LENGTH: 95
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13
gctgaatgtatccac taactgagca gtcagtagtt ggtccttgg ttgcataatga      60
tgcgataatt gtttcaagac gggactgtatgc gcagc                                         95

<210> SEQ ID NO 14
<211> LENGTH: 126
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14
tcccaatgaa gaaactttca catgtcttac tctctgtccct agtcccagag cctgtaaagg      60
tgaacccact gggactggct gggggagaag aggaagattt gttccagaag gaactgtctg      120
aggat                                         126

<210> SEQ ID NO 15
<211> LENGTH: 110
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15
tgcccagtga tgacaccatc cttgtcccc gtcgtatgg gggctatgg gcgacaccat      60
ggctgccccct gggctggcc agtggggcca atgcccagggg gctgaggggca      110

<210> SEQ ID NO 16
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16
tgcagatgtatgatgaaat atttgctatc tgagagatgg tgatgacatt ttaaaccacc      60
aagatcgctg atgca                                         75

<210> SEQ ID NO 17
<211> LENGTH: 67
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

```

-continued

ttcctatgt gaggacctt tcacagacct gtactgagct ccgtgaggat aaataactct 60
 gaggaga 67

<210> SEQ ID NO 18
 <211> LENGTH: 75
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18
 ctacggggat gatttacga actgaactct ctctttatga tggatttagtg gagaaaacag 60
 aaaattctga gtagc 75

<210> SEQ ID NO 19
 <211> LENGTH: 72
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19
 actccatgt gaacacaaaa tgacaagcat atggctgaac tttcaagtga tgtcatctta 60
 ctactgagaa gt 72

<210> SEQ ID NO 20
 <211> LENGTH: 75
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20
 gtcagatgt ttgaattgt aagctgatgt tctgtgaggt aaaaaagtta atagcatgtt 60
 agagttctga tggca 75

<210> SEQ ID NO 21
 <211> LENGTH: 65
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21
 tttctatgt gaatcaaact agctcaactt gaccgacagt gaaaatacat gaacacctga 60
 gaaac 65

<210> SEQ ID NO 22
 <211> LENGTH: 70
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22
 gtttgtatg acttacatgg aatctcggtc ggctgatgac ttgctgttga gactctgaaa 60
 tctgattttc 70

<210> SEQ ID NO 23
 <211> LENGTH: 71
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23
 ctcaccagtg atgagttgaa taccggccca gtctgatcaa tgtgtgactg aaaggtattt 60
 tctgagctgt g 71

<210> SEQ ID NO 24

-continued

```

<211> LENGTH: 77
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24
gtcagtatg agcaacattc accatcttc gttttagtct cacggccatg agatcaaccc      60
catgcaccgc tctgaga                                         77

<210> SEQ ID NO 25
<211> LENGTH: 77
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25
attggatg agcaacaatc accatcttc gttttagtct catggccatg agaccaaccc      60
catgcactgc tctgaga                                         77

<210> SEQ ID NO 26
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26
cgccatgat gttccgcaac tacctacatt gttttagtct catgaaagca gcactggctg      60
agacgc                                         66

<210> SEQ ID NO 27
<211> LENGTH: 86
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27
ggcagatgat gtccttatct cacgatggtc tgcggatgtc cctgtggaa tggcgacaaat      60
gccaatggct tagctgatgc caggag                                         86

<210> SEQ ID NO 28
<211> LENGTH: 88
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28
tggcagatga tgtttgttt cacgatggtc ttcagatgcc cacgtggca ctgctgagaa      60
agccacttgg taaaactgat gccggaaa                                         88

<210> SEQ ID NO 29
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29
ttgcaatgat gtgaatctct cactgaattc aaccttgaaat tgcgaatcca tgagtttt      60
aacccctgagc aa                                         72

<210> SEQ ID NO 30
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30
gttgcgttga tgtaaaattt cttggcctga aattactgtg aagagtaaaa ccgagcttt      60

```

-continued

taacactgag t	71
<210> SEQ ID NO 31	
<211> LENGTH: 68	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 31	
ttgccaatga tggtaagaa tttttcacc tgaataaacc atgtggtcag cattgcac	60
gaggcaaa	68
<210> SEQ ID NO 32	
<211> LENGTH: 66	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 32	
attcgatgtt actgatcatt ttttactttt gaccagatgt ctactgaaga aagcctgcgt	60
ctgagg	66
<210> SEQ ID NO 33	
<211> LENGTH: 71	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 33	
tttcgtat gaaaactctg tccagttctg ctactgaagg gagagagatg agagecttt	60
aggctgagga a	71
<210> SEQ ID NO 34	
<211> LENGTH: 69	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 34	
tctcgtat gaaaactttt tccagttctg ctactgacag taagtgaaga taaagtgtgt	60
ctgaggaga	69
<210> SEQ ID NO 35	
<211> LENGTH: 70	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 35	
tggaaatgttgacacccgt gactgttcatgtt gtggaaatgttgacacccgt attcgatctg	60
gtgtatccatgtt	70
<210> SEQ ID NO 36	
<211> LENGTH: 58	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 36	
aatgtatggaa aaatcattat tggaaaagaa tgacatgaac aaaggaacca ctgaatgt	58
<210> SEQ ID NO 37	
<211> LENGTH: 67	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	

-continued

<400> SEQUENCE: 37

```
gtgcatatga tggaaaagtt ttaatctcct gacacttgc atgtcttcaa aggaaccact      60
gatgcac                                         67
```

<210> SEQ ID NO 38
<211> LENGTH: 62
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

```
cacagatgtt gaaacttattt acggggcgac agaaaactgtg tgctgattgt cacgttctga      60
tt                                         62
```

<210> SEQ ID NO 39
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

```
cctggatgtt gataaggcaaa tgctgactgtt acatgttgggtt cttttttttt tctttttttt      60
taa                                         63
```

<210> SEQ ID NO 40
<211> LENGTH: 83
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

```
ggtaatgtt gtgttggcat gtattatctg aatctattgtt tgatgtgtttt taacactttt      60
gtcttagaat tactctgaga cct                                         83
```

<210> SEQ ID NO 41
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

```
ggtaatgtt gtaatggcat gtattatctg aatctaaatgtt tgatgtgtttt tctttttttt      60
cactgagacc t                                         71
```

<210> SEQ ID NO 42
<211> LENGTH: 78
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

```
ggtaatgtt gagttggcat gtattatctgaa tctaaatgtt attattacta ctttagctct      60
agaattttttt ttggaccc                                         78
```

<210> SEQ ID NO 43
<211> LENGTH: 98
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

```
gtagggtgtt gaaaaagaat ctttagggcggtt gggttgtggcc gtcttggtca cctgtgtgcc      60
acttgccat gcaaggactt gtcataatgtt cactgtgtt                                         98
```

-continued

<210> SEQ ID NO 44
<211> LENGTH: 65
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

taatgattct gccaaatgaa atataatgtat atcactgtaa aaccgttcca ttttgattct 60
gaggt 65

<210> SEQ ID NO 45
<211> LENGTH: 64
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

agtgatgtatg accccaggta actcttgagt gtgtcgctga tgccatcacc gcagcgctct 60
gacc 64

<210> SEQ ID NO 46
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

tgtctgtatg aaatcaactaa taggaagtgc cgtcagaagc gataactgac gaagactact 60
cctgtctgtat 71

<210> SEQ ID NO 47
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

ctgatgatac ttgtaatagg aagtggcgatc agaagcgata actgacga 48

<210> SEQ ID NO 48
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

tatctgtatg gatcttatcc cgaacctgaa ctctgttga aaaaaaaaaa cttttacggaa 60
tctggcttct gagat 75

<210> SEQ ID NO 49
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

taatcaatga tgaaaacctat cccgaagctg ataacctgaa gaaaaataag tacggattcg 60
gcttctgaga t 71

<210> SEQ ID NO 50
<211> LENGTH: 70
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

gttgcgtatg gaataaaatc aaatcacat ctttcggctg agttcgatg ggatttgctt 60

US 9,273,294 B2

45**46**

-continued

ttttctgatt

70

<210> SEQ ID NO 51
<211> LENGTH: 64
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

ggaaatgatg attcacaga ctagagtctc cgatgctgg catgatgtca aaactaagtt 60
ctga 64

<210> SEQ ID NO 52
<211> LENGTH: 78
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

atgctatgat gacatccata tggttcgct gctggctgag tttcagagat gacaccatcc 60
tcttggctgt ctgagcat 78

<210> SEQ ID NO 53
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

tggcgatgag gaggtaccta ttgtgttgag taacggtgat aattttatac gctattctga 60
gcc 63

<210> SEQ ID NO 54
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

ccacaatgat ggcaatattt ttctgtcaaca gcagttcacc tagtgagtgt tgagactctg 60
ggtctgagtg a 71

<210> SEQ ID NO 55
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

tggagggtgat gaactgtctg agcctgacct tgtagaatgg aggcaaaaaa actgatttaa 60
tgagcctgat cc 72

<210> SEQ ID NO 56
<211> LENGTH: 65
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

ctgcagtgat gactttctta ggacacctt ggatttaccc tgaaaattaa taaattctga 60
gcagc 65

<210> SEQ ID NO 57
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 57
ctgcgatgt ggcatttctt aggacacctt tggattaata atgaaaacaa ctactctctg 60
agcagc 66

<210> SEQ ID NO 58
<211> LENGTH: 65
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58
ttgctgtat gactatctta ggacacctt ggaataacta tgaaagaaaa ctattcttag 60
caacc 65

<210> SEQ ID NO 59
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59
ccttctatga tgattttatc aaaatgactt tcgttcttct gagtttgctg aagccacatt 60
taggtactga gaagg 75

<210> SEQ ID NO 60
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60
tattcctcac tcatgagttac gttctgactt tcgttcttct gagtttgctg aagccagatg 60
caatttctga gaagg 75

<210> SEQ ID NO 61
<211> LENGTH: 83
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61
agtctgtat gaattgctt gacttctgac acctcgatg aaaactgcac gtgcagtc 60
attattnac aagactgagg ctt 83

<210> SEQ ID NO 62
<211> LENGTH: 73
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62
gctatgtatgatgatgatgc attgatcgatc tgacatgata atgtatcccc gtcctctaag 60
aagttctgag ctt 73

<210> SEQ ID NO 63
<211> LENGTH: 86
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63
tctcagtgat gtaattccaa tagatcccttc tgaccctcca ctgtggactc aatagcagg 60
agatgaagag gacagtgactc gagaga 86

US 9,273,294 B2

49**50**

-continued

```

<210> SEQ ID NO 64
<211> LENGTH: 86
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64
tctcagtat gtaattccaa tagatccttc tgaccctcca ctgtggactc aatagcaggg      60
agatgaagag gacagtgact gagaga                                         86

<210> SEQ ID NO 65
<211> LENGTH: 68
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65
gtgcaatgtat gtatTTATT caacacatca ttctgaaaga acgtgtggaa aactaatgac      60
tgagcaca                                         68

<210> SEQ ID NO 66
<211> LENGTH: 67
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66
ggatTTgtga tgagctgtgt ttactgagca tcatgaaatgt aagctcaacg tgattactct      60
gaagtcc                                         67

<210> SEQ ID NO 67
<211> LENGTH: 73
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67
aaatgatgaa atcacccaaa atagctggaa ttacccggcag attgtgttgt ggtgaactca      60
tggTTTctg aag                                         73

<210> SEQ ID NO 68
<211> LENGTH: 76
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68
ttcctctgtat gacttcctgt tagtgccacg tgtctggcc actgagacac catgtatggaa      60
ctgaggatct gaggaa                                         76

<210> SEQ ID NO 69
<211> LENGTH: 111
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69
tgtgagatgt atgagttgca cactgggtga gccatggtat caggtgatac aggcaccact      60
cagtatcacc ctggtgacaa aatcaagtgc acaggggcca tctgactcac a             111

<210> SEQ ID NO 70
<211> LENGTH: 77
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

```

-continued

aatgtgaagc aaatgatgat aaactggatc tgactgactg tgctgagtct gttcaatcca	60
accctgagct tcatgtt	77

<210> SEQ ID NO 71
<211> LENGTH: 88
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

ttcgttgttgc caatgatgtt attttcttg gaactgaatc taagtgatct gactcaatata	60
tcgtcactac cactgagaca acgtgaa	88

<210> SEQ ID NO 72
<211> LENGTH: 86
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

tgtgtgttgg aggtgaaag tacggagtga tccatcggtt aagtgtcttg tcacaatgct	60
gacactcaaa ctgtcacatg cacacg	86

<210> SEQ ID NO 73
<211> LENGTH: 80
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

agcttatcag tcatgttgc aaaataatgt tctgaacata tgaatgcagt attgattca	60
gcatttaact gagataagcg	80

<210> SEQ ID NO 74
<211> LENGTH: 65
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

aataagtgtt gaaaaaaatgg ttccgtcccag atgatggcca gtgataacaa cattttctg	60
atgtt	65

<210> SEQ ID NO 75
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

aatgaatgtt gacaaaatgtt ttcagtccca aatgatacat actgattata ccattatatt	60
tatcctgaca ttctt	75

<210> SEQ ID NO 76
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

ctgcctctgtt gaaaggctgtt gttggtaggg acatctgaga gtaatgttga atgccaaccg	60
ctctgatggt gg	72

<210> SEQ ID NO 77

-continued

```

<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

agcctgtat gcttaagag tagtggacag aagggatttc tgaaattcta ttctgaggct      60

<210> SEQ ID NO 78
<211> LENGTH: 80
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

gccacaatga tgacagttt tttgtactc ttgagtgtca gaatgtatgag gatcttaacc      60
accattatct taactgaggc                                         80

<210> SEQ ID NO 79
<211> LENGTH: 70
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

agatactatg atgggttgcatt agttcagcag attaatcat gaagagatgt actatctgtc      60
tgatgtatct                                         70

<210> SEQ ID NO 80
<211> LENGTH: 65
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

gtgtatgtatgat gtttatcaaa tgtctgacct gaaatgagca tgttagacaaa ggtaacactg      60
aagaaa                                         65

<210> SEQ ID NO 81
<211> LENGTH: 85
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

tactgttagt gatgattttt aaattaaagc agatggaaat ctctctgaga aagaaaatgg      60
agattaatct taaactgaaa cagta                                         85

<210> SEQ ID NO 82
<211> LENGTH: 78
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

gatacaatga tgataacata gttcagcaga ctaacgctga tgagcaatat taagtcttc      60
gctcctatct gatgtatc                                         78

<210> SEQ ID NO 83
<211> LENGTH: 77
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

cagaatacat gatgatctca atccaaacttg aactctctca ctgattactt gatgacaata      60
aaatatctga tattctg                                         77

```

-continued

```

<210> SEQ ID NO 84
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84
acagcacaaa tcatgtataaa caaaaggact taataactgaa acctgtatgtt acattgtatgt 60
gtgtgtatgtt gctgt 75

<210> SEQ ID NO 85
<211> LENGTH: 95
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85
gctgttcgtt gatgaggcgc agagttagcg ctgggtacag cgcccaatc ggacagtgtta 60
gaaccattctt ctactgcctt ccttctgaga acagc 95

<210> SEQ ID NO 86
<211> LENGTH: 93
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86
gctgttcgtt gatgaggcctt ggaatgtcgctt ctgggcacag cgcccgagac agactgcgg 60
accgttcctt gttgccttcc ttctgagaac agc 93

<210> SEQ ID NO 87
<211> LENGTH: 78
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87
cccatatgtt gttttttttt cgaaagggtga ggcgtttcgctt cagtgtatgac cctcatctat 60
cccccttgac tcatggct 78

<210> SEQ ID NO 88
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88
gactggcaag gatgatacac actgtccctc acttagacta tagttcactg atgagagcat 60
tggcttgac cagtc 75

<210> SEQ ID NO 89
<211> LENGTH: 86
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89
gatcacggtg atggctgacc agggctccct gacctataca ggctctgtt atgggggtga 60
tggccagtc tgggtctgtt gtgtt 86

<210> SEQ ID NO 90
<211> LENGTH: 76
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

<400> SEQUENCE: 90
 acaatgatga cttaaattac ttttgcgt ttacccagct gaggttgtct ttgaagaaat 60
 aatttaaga ctgaga 76

<210> SEQ ID NO 91
 <211> LENGTH: 97
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91
 cggggcctc catgatgtcc agcaactggc tccgactgcc actgaggaca cggtgcccc 60
 cgggacctt gacacccggg ggtctgaggg gccctgg 97

<210> SEQ ID NO 92
 <211> LENGTH: 97
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92
 ttggggaccc cgtgatgtcc agcaactggc tctgactgcc cctgaggaca cggtgcaccc 60
 cgggacctt gacatccggg gttctgaggg gccccac 97

<210> SEQ ID NO 93
 <211> LENGTH: 97
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93
 ctggggctcc catgatgtcc agcaactggc tctgatcacc cctgaggaca cagtgcaccc 60
 caggacctt gacacctggg ggtctgaggg gccccag 97

<210> SEQ ID NO 94
 <211> LENGTH: 114
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94
 atcgaggaat gatgacaaga aaaggccgaa ttgcagtgtc tccatcaga gtttgctctc 60
 catggcaca cgatgacaaa atatcctgaa gcgaaccact agtctgacct cagt 114

<210> SEQ ID NO 95
 <211> LENGTH: 107
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95
 aagtttcta agtgtcta at gatgaatttc ataggcaga ttctgaggtg aaaatttat 60
 tcatcaactga tactctact gtggaatctg aagacacttg aaaacgt 107

<210> SEQ ID NO 96
 <211> LENGTH: 92
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96
 tagagaagtc aatgatggtt ttattcatat cgtctgaacc tgtctgaagc atctcaagtga 60
 tgcaatctct gtgtggttct gagacttctc ca 92

US 9,273,294 B2

59**60**

-continued

```

<210> SEQ ID NO 97
<211> LENGTH: 86
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97
aagagccat gatgtttta ttcaaatgt ctgaacctgt ctgaaggatc ccagtatgc      60
aacttctgtg tgatactgag gctttt                                         86

<210> SEQ ID NO 98
<211> LENGTH: 89
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98
tggtgctgtg atgatgcctt aatattgtgg tttcgactca ctgagatcaa aatgaggacc      60
tacaattcct tggctgtgtc tgagcacccc                                     89

<210> SEQ ID NO 99
<211> LENGTH: 74
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99
tggccaagga tgagaactct aatctgattt tatgtgcttc tgctgtatg gattaaagga      60
tttacctgag gccaa                                         74

<210> SEQ ID NO 100
<211> LENGTH: 137
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100
caggctgtga tgattggcgc aggggtacgg acctcagctg agtcatggga gctgaatgt      60
tgtgtttctc ctttgtcctg catgtggcag gctgatgggg agcacttaca tgagactgtt     120
gcctcaatct gaggctg                                         137

<210> SEQ ID NO 101
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101
gcgggtatga ccccaacatg ccatctgagt gtcgggtctg aaatccagag gctgtttctg      60
agc                                         63

<210> SEQ ID NO 102
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102
cctgggtatg acagatggca ttgtcagcca atccccaaatg gggagtgagg acatgtcctg      60
caattctgaa gg                                         72

<210> SEQ ID NO 103
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

US 9,273,294 B2

61**62**

-continued

<400> SEQUENCE: 103

cctggtgatg acagacgaca ttgtcagcca atccccatgt ggtagtgagg acatgtcctg	60
cagttctgaa gg	72

<210> SEQ ID NO 104

<211> LENGTH: 142

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

ttgcccgtat attataaaaa gacgcgttat taagaggact ttatgttggaa gttcttgacg	60
tttttctctc ttttctatac ttctttttct ttctttgaat gtccagcgctc ctgtgagcga	120
agattatgat atatgagggc aa	142

<210> SEQ ID NO 105

<211> LENGTH: 67

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

gagtttatgtat gtgtgttaat cctattccat tgctgaaatg cagtgtggaa cacaatgaac	60
tgaactc	67

<210> SEQ ID NO 106

<211> LENGTH: 80

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

actgggtccag gatgaaacctt aattttagtg gacatccatg gatgagaaat gcggatatgg	60
gactgagacc agctcctagg	80

<210> SEQ ID NO 107

<211> LENGTH: 76

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

gctgtacatg atgacaactg gctccctcta ctgaactgcc atgagggaaac tgccatgtca	60
cccttctgtat tacagc	76

<210> SEQ ID NO 108

<211> LENGTH: 73

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

gtttgaatga tgactttaat tgtcgatcac cccttcactc cttttatgag tgaaaacataa	60
gagtcgtaca aac	73

<210> SEQ ID NO 109

<211> LENGTH: 72

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

agcttaatga tgactgtttt ttttgattgc ttgaagcaat gtgaaaaaca catttcacccg	60
gctctgaaag ct	72

-continued

```

<210> SEQ ID NO 110
<211> LENGTH: 91
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110
ttgtctggca atgatgaccc acttgcctc actgagaaca aagttcggt a t g a g a a t c t      60
ttgttaatgg actcaagg ttc tgagccagac a                                         91

<210> SEQ ID NO 111
<211> LENGTH: 91
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111
ttgtctggca atgatgaccc acttgcctc actgagaaca aagttcggt a t g a g a a t c t      60
ttgttaatgg actcaagg ttc tgagccagac a                                         91

<210> SEQ ID NO 112
<211> LENGTH: 80
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112
ggcctgctgt gatgacattc caattaaagc acgtgttaga ctgctgacgc gggtgatgcg      60
aactggagtc tgagcctgcc                                         80

<210> SEQ ID NO 113
<211> LENGTH: 85
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113
cccctatctc tcatgatgaa cacatatgcc tctgagctgc tgtgatttct ggcttcaaag      60
taaacgcgtct gaagaagaga tgggg                                         85

<210> SEQ ID NO 114
<211> LENGTH: 79
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114
ccacatgcgg ctgatgacag cacttctgtc gagacgctgt gattgctctg tccaaagtaa      60
acgcccgtac gcactgtgg                                         79

<210> SEQ ID NO 115
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115
ggttcatgt gacacaggac cttgtctgaa cataatgatt taaaaattt agcttaaaaa      60
tgacactctg aaatc                                         75

<210> SEQ ID NO 116
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

-continued

<400> SEQUENCE: 116

```
gcttaatgt gagaatcatt atttcttgaa ttggatgaca ctttccattc ctgcaaaggg      60
agcgtgaggt c                                         71
```

<210> SEQ ID NO 117
<211> LENGTH: 67
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

```
ggatcgatga tgagaataat tgtctgagga tgctgaggga ctcattccag atgtcaatct      60
gaggtcc                                         67
```

<210> SEQ ID NO 118
<211> LENGTH: 67
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

```
ggatcgatga tgagaataat tgtctgagga tgctgaggga ctcattccag atgtcaatct      60
gaggtcc                                         67
```

<210> SEQ ID NO 119
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

```
ttgcagtgt gacttgcgaa tcaaattctgt caatccccgt agtgcaatca ctgatgtctc      60
catgtctctg agcaa                                         75
```

<210> SEQ ID NO 120
<211> LENGTH: 94
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

```
cagcctgaaa ttagtactt taaaaaaatt tcatgtctct tctctgacat ttttctctgg      60
acacagttt tgccttatga atctgatcag gctg                                         94
```

<210> SEQ ID NO 121
<211> LENGTH: 87
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

```
cagcctgaag ttagtattca cattcatgtc ttttctctga taaattcttg aagaaaattt      60
tttgtgtctt gatcaggcct ctagagg                                         87
```

<210> SEQ ID NO 122
<211> LENGTH: 77
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

```
tggccaatg atgagacagt gtttatgaac aaaagatcat gattaatcca gttctgcaca      60
aaacactgag gtccatt                                         77
```

-continued

```

<210> SEQ ID NO 123
<211> LENGTH: 70
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123
aaaagttagtg atgaatagtt ctgtggcata tgaatcatta atttttagtta aaccctaaac      60
tctgaagtcc                                         70

<210> SEQ ID NO 124
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124
atagccaatc attagttttc tgagctgttag gaatcaaaga ttttgattttt attctgttac      60
tcagaggttt a                                         71

<210> SEQ ID NO 125
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125
tagaccaatg atgagttttc tggggtgtct gaatcaatga ttttgattttt accctgttac      60
tctgagggtcc a                                         71

<210> SEQ ID NO 126
<211> LENGTH: 74
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126
tggaccaatg atgagtttac tggggtatct gaaacaggat ttttgattttt acccatatgc      60
aattctgagg tcca                                         74

<210> SEQ ID NO 127
<211> LENGTH: 77
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127
tggatcaatg atgagttttg gtggagggtgt ctgaatcaac actttttttt aagccctctg      60
tgtaactctg agatctg                                         77

<210> SEQ ID NO 128
<211> LENGTH: 74
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128
tggaccagggtg atgaatatca tggggtttct gaaacaacat ttttgattttt acccatctgc      60
aactctgagg tcca                                         74

<210> SEQ ID NO 129
<211> LENGTH: 76
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

```

US 9,273,294 B2

69**70**

-continued

tggatcaatg atgagtatgc gtggggcattc tgaatcaaata ttctgttaccc 60

gtatctctga ggtcca 76

<210> SEQ ID NO 130

<211> LENGTH: 73

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

tggaccaatg atgagattgg agggtgtctg aatcaaaaat tttgattaaa gccatctgt 60

actctgaggta cca 73

<210> SEQ ID NO 131

<211> LENGTH: 71

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

tggatcaatg atgagtatcc tgggtgtctt gaatcttggaa ttttGattaa accctataac 60

tctgaggta c 71

<210> SEQ ID NO 132

<211> LENGTH: 71

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

tggacctatg atgatgactg gtggcgtagt agtcatttac ggtgaataaca ggtctggaa 60

tctgaggta c 71

<210> SEQ ID NO 133

<211> LENGTH: 77

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

gggaccaatg ataatgactg ttgggtatg agtcagttagt gttgaataac agtttgatc 60

tggaaatctg aggtcca 77

<210> SEQ ID NO 134

<211> LENGTH: 74

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

tggaccaatg atgaccactg gtggcgttt agtcattttac gatgaataact acgtgtctgt 60

aactctgagg tcca 74

<210> SEQ ID NO 135

<211> LENGTH: 74

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

tgagccatgt atgaaaactg gtggcataga agtcaaggat gctgaataat gtgtgtctgt 60

aactctgagg ttca 74

<210> SEQ ID NO 136

<211> LENGTH: 69

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

tggattgatg atgaccactg gtggcctatg agtcatacaa tgaatacgtg tctagaactc	60
tgagggtcca	69

<210> SEQ ID NO 137
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

tggatcaatg atgtccactg gtggcgtaa aatcatattt ggtgaatata tgtctggAAC	60
tctgagggtcc a	71

<210> SEQ ID NO 138
<211> LENGTH: 76
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

tgaactagtg gtgatggctt gtggcatatt tagtcacaga tcatgtataa atacatgcct	60
gagactctga ggtag	76

<210> SEQ ID NO 139
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

tcatgtatag atggccactg gtggcttatg agtcttatac agtgaataca tggtttgaaAC	60
tctgagggtct g	71

<210> SEQ ID NO 140
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

tggatcgatg atgactgctg gtggcgatg agtcttacat gatgaatacg tgtctggAAC	60
tctgagggtcc a	71

<210> SEQ ID NO 141
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

aagatcaatg atgactactg ttatgtatg agttacacat gatgaataca tgtctgAAAC	60
tctgagggtcc a	71

<210> SEQ ID NO 142
<211> LENGTH: 74
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

tggaccagtg atggtgactg gtgggtgtgtg agtcatgcac agtgaatatac atgtgtctgg	60
---	----

-continued

aactctgagg tcca	74
<210> SEQ ID NO 143	
<211> LENGTH: 74	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 143	
tggaccaatg atgacaataa ccggcgatg agtcttggat gatgaataat acgtgtctgg	60
aactctgagg tcca	74
<210> SEQ ID NO 144	
<211> LENGTH: 73	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 144	
tggaccagtg atgaccactg gtggcatatg agtcatacac atgaacacca tgtttctaga	60
aactctgaggt cca	73
<210> SEQ ID NO 145	
<211> LENGTH: 74	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 145	
tggaccaatg atgacaactg ccggcgatg agtggtgggt gatgaataat acgtgtctag	60
aactctgagg tcca	74
<210> SEQ ID NO 146	
<211> LENGTH: 71	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 146	
tggatcgatg atgaccactg gtggcgatg agtcatacat gatgaatatg tgtctggAAC	60
tctgaggTcc t	71
<210> SEQ ID NO 147	
<211> LENGTH: 69	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 147	
tggaccaatt atgactactg gtgtgagtcA cgccataatga acaccacgtg tctggAACTC	60
tgaggGTCCA	69
<210> SEQ ID NO 148	
<211> LENGTH: 74	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 148	
tggaccaatg atgacaaatg gtggcattgg agttatggac gatgaatgtat atgtgtctga	60
aactctgagg tcca	74
<210> SEQ ID NO 149	
<211> LENGTH: 71	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	

-continued

<400> SEQUENCE: 149

tagatcaatg atgactactg ttgggttatg agtcataaac gatgaataaca tgtctgaaat	60
tctgagggcc a	71

<210> SEQ ID NO 150

<211> LENGTH: 74

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

tggatcaatg ataaaacttg ctggcatatg aatcttggat aatggatgt acgtgtgtgg	60
aactctgagg tcca	74

<210> SEQ ID NO 151

<211> LENGTH: 71

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

tggatcgatg atgactactg gtggcgtatg agtcatctac agtgaataacg tctctggAAC	60
tctgagggtct g	71

<210> SEQ ID NO 152

<211> LENGTH: 71

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

tggatcaatg atgaccactg gtggcgtatg agtcatatgt gatgaataacg tgtctggAAC	60
tctgagggtcc a	71

<210> SEQ ID NO 153

<211> LENGTH: 71

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

tggatcgatg atgactaccg gtggcgtatg agtcatatgt gatgaataacg tgTTTggAAC	60
tctgagggtcc a	71

<210> SEQ ID NO 154

<211> LENGTH: 71

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

tggatcgatg atgactactg gtggcgtatg agtcataAGAC aatgaataacg tgtctggAAC	60
tctgagggtcc a	71

<210> SEQ ID NO 155

<211> LENGTH: 71

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

tggatcgatg gtgactgttg atggcatatg actcacatAT gatgagtacg tatctggAAC	60
tctgagggtct g	71

-continued

```

<210> SEQ ID NO 156
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156
tggatcgatg atgactactg gtggcgtatg agtctttgc gatgaatacg tgtctagaac      60
tctgagggtcc g                                         71

<210> SEQ ID NO 157
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157
tggatcgatg atgagcactg gtggagtagt agtcacatac gatgaatacg tgtctgaaac      60
tctgagggtcc a                                         71

<210> SEQ ID NO 158
<211> LENGTH: 69
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158
tggttcagtg ttgactactg gtgtcgtgtg agtcatacaa tgaatacatg tctggaactc      60
tgaggccca                                         69

<210> SEQ ID NO 159
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159
tggatcgatg atgactgctg gtggcgtatg agtcatatgc gatgaatacg tgtctagaac      60
tctgagggtcc a                                         71

<210> SEQ ID NO 160
<211> LENGTH: 69
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 160
tggatcgatg atgactactg gtagcatgag tcataatacg tgaatacatg tctggaactc      60
tgaggtctg                                         69

<210> SEQ ID NO 161
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161
tggatcaatc atgactactg gtattggatg ggtcttcgtc agtgaatgcc tatctgaaac      60
tctgagggtcc a                                         71

<210> SEQ ID NO 162
<211> LENGTH: 74
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

```

-continued

tgagcaagcg atgacagccg gtggtgtgtg agtcatggag gatgaatact aagtgcctgg	60
aactctgagg ttca	74
<210> SEQ ID NO 163	
<211> LENGTH: 97	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 163	
tggatcgatg atgagtcccc tataaaaaca ttccttgaa aagctgaaca aaatgagtga	60
gaactcataa cgtcattctc atcggaaactg aggtcca	97
<210> SEQ ID NO 164	
<211> LENGTH: 97	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 164	
tggatcgatg atgagtcccc aaaaaaaaca ttccttgaa aagctgaaca aaatgagtga	60
aaactcatac cgtcattctc atcggaaactg aggtcca	97
<210> SEQ ID NO 165	
<211> LENGTH: 97	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 165	
tggatcgatg atgagtcccc cataaaaaca ttccttgaa aagctgaaca aaatgagtga	60
gaactcatac cgtcgttctc atcggaaactg aggtcca	97
<210> SEQ ID NO 166	
<211> LENGTH: 98	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 166	
tggatcgatg atgagtcccc ccaaaaaaac attccttggaa aaagctgaac aaaatgagtg	60
aaaactcata ccgtcggtct cagcgaaact gaggtcca	98
<210> SEQ ID NO 167	
<211> LENGTH: 97	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 167	
tggatcgatg atgagtcccc cataaaaaca ttccttgaa aagctgaaca aaatgagtga	60
gaactcatac cgtcgttctc atcagaactg aggtcca	97
<210> SEQ ID NO 168	
<211> LENGTH: 97	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 168	
tggatcgatg atgagtcccc cataaaaaca ttccttgaa aagctgaaca aaatgagtga	60
gaactcatac cgtcgttctc atcagaactg aggtcca	97
<210> SEQ ID NO 169	

-continued

<211> LENGTH: 97
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

tggatcgatg atgagtccctc caaaaaaaca ttcccttggaa aagctgaaca aaatgaggta	60
gaactcatac cgtcgttctc atcggaaactg aggtcca	97

<210> SEQ ID NO 170
<211> LENGTH: 97
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

tggatcgatg atgagtcccc cataaaaaaca ttcccttggaa aagctgaaca aaatgaggta	60
gaactcatac cgtcgttctc atcggaaactg aggtcca	97

<210> SEQ ID NO 171
<211> LENGTH: 104
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

taggttgatg atgacttaca tatatacggtt tttttttttt ttttggaaag gtgaacaaaa	60
ttagtgaaaa ctcagtagcca tcatcctcat ctaactgagg tcca	104

<210> SEQ ID NO 172
<211> LENGTH: 94
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

tggatcaatg atgacttcca tacgtgggtt ccttggaaag ttgaacaaaa tgagtgaaaa	60
ctttatactg tcatcctctt caaactgagg tcca	94

<210> SEQ ID NO 173
<211> LENGTH: 94
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

tggatcaatg atgacttcca tatatacatt ccttggaaag ctgaataaaa tgaatgaaaa	60
ctctataccca tcatcctcat tgaactgagg tccc	94

<210> SEQ ID NO 174
<211> LENGTH: 94
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

tggaccaatg atgacttcca tacatgcatt ccttggaaag ctgaacaaaa tgagtggaa	60
ctctgtacta tcatcttagt tgaactgagg tcca	94

<210> SEQ ID NO 175
<211> LENGTH: 94
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

tggatcgatg atgacttcca tatatacatt ccttggaaag ctgaacaaaa tgagtgaaaa	60
---	----

-continued

ctctataccg tcatttcgt cgaactgagg tcca	94
<210> SEQ ID NO 176	
<211> LENGTH: 94	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 176	
tggatcgatg atgacttcca tatatacatt cttggaaag ctgaacaaaa tgagtgaaaa	60
ctctataccg tcatcctcggt ccaaactgagg tcca	94
<210> SEQ ID NO 177	
<211> LENGTH: 94	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 177	
tggatcgatg atgacttcca tacatgcatt cttggaaag ctgaacaaaa tgagtgaaaa	60
ctctataccg tcatcctcggt cgaactgagg tcca	94
<210> SEQ ID NO 178	
<211> LENGTH: 94	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 178	
tggatcgatg atgacttcca tatatacatt cttggaaag ctgaacaaaa tgagtgaaaa	60
ctctataccg tcatcctcggt cgaactgagg tcca	94
<210> SEQ ID NO 179	
<211> LENGTH: 94	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 179	
tggatcgatg atgacttccc tatatacatt cttggaaag ctgaacaaaa tgagtgaaaa	60
ctctataccg tcatcctcggt cgaactgagg tcca	94
<210> SEQ ID NO 180	
<211> LENGTH: 94	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 180	
tggatcgatg atgacttcca tatatacatt cttggaaag ctgaacaaaa tgagtgaaaa	60
ctctataccg tcatcctcggt cgaactgagg tcca	94
<210> SEQ ID NO 181	
<211> LENGTH: 94	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 181	
tggatcgatg atgacttcca tatatacatt cttggaaag ctgaacaaaa tgagtgaaaa	60
ctctataactg tcatcctcggt cgaactgagg tcca	94
<210> SEQ ID NO 182	
<211> LENGTH: 94	
<212> TYPE: DNA	

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

tggatcgatg atgacttcca catatacatt ccttggaaag ctgaacaaaa tgagtgaaaa	60
ctctataccg tcatacctcg tcaactgagg tcca	94

<210> SEQ ID NO 183

<211> LENGTH: 94

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

tggatcgatg atgacttcca tatgtacatt ccttggaaag ctgaacaaaa tgagtgaaaa	60
ctctataccg tcatacctcg tcaactgagg tcca	94

<210> SEQ ID NO 184

<211> LENGTH: 94

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

tggatcgatg atgacctcaa tacatgcatt ccttggaaag ctgaacaaaa tgagtgaaaa	60
ctctataccg tcgtcctcg tcaactgagg tcca	94

<210> SEQ ID NO 185

<211> LENGTH: 94

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

tggatcgatg atgactttta tacatgcatt ccttggaaag ctgaacaaaa tgagtgaaaa	60
ctctataccg tcatacctcg tcaactgagg tcca	94

<210> SEQ ID NO 186

<211> LENGTH: 94

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

tggatcgatg atgactttaa aatggatctc atcggaatct gaacaaaatg agtgaccaaa	60
tcaacttcgt gccacttctg tgagctgagg tcca	94

<210> SEQ ID NO 187

<211> LENGTH: 98

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

tggatcgatg atgactataa aaaaaatgga tctcatcgga atctgaacaa aatgagtgac	60
caaatcattt ctgtgccact tctgtgagct gaggtcca	98

<210> SEQ ID NO 188

<211> LENGTH: 94

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188

tggatcgatg atgacttaaa gatttatcta atttaaatct gaacaaaatg agtgaccaaa	60
acacttctgt accacttctg tgagctgagg tcca	94

<210> SEQ ID NO 189
<211> LENGTH: 93
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

tggatggatg acgacttaaa aatgaatctc gttggaatct gagcaaaaacg agtgagcaaa	60
ccacttctgt gcagttctgt gaactgaggt caa	93

<210> SEQ ID NO 190
<211> LENGTH: 85
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

tggatcgatg atgacttaaa aaaatggaaa cttggaaat ctgaacaaaa tgagtgcacca	60
agacacttct gtgagctgag gtcca	85

<210> SEQ ID NO 191
<211> LENGTH: 98
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

tggatecgatg atgagtccctc caaaaaaaaaac attccttggaa aagctgaac aaaatgagtg	60
aaaactcata ccgtcattct catcgaaact gaggtcca	98

<210> SEQ ID NO 192
<211> LENGTH: 76
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

gccaaatgtatgtttaaacaggagca ctcagtgca aggacgactc ttatctatca	60
cccatgactg atggct	76

<210> SEQ ID NO 193
<211> LENGTH: 136
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193

atcgctcagggt gggataatcc ttacctgttc ctccctccgga gggcagatataa acatgtatgt	60
attggagatg catgaaacgt gattaacgtc tctgcgtaat caggacttgc aacaccctga	120
ttgcctctgt ctgatt	136

<210> SEQ ID NO 194
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194

gctggattaa tgatgagata taaccttgcac tgaagctgat gatgagtttg tataattaag	60
caggattact ctgagatcca gc	82

<210> SEQ ID NO 195
<211> LENGTH: 90
<212> TYPE: DNA

US 9,273,294 B2

89**90**

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

cttagtccag aaaacaatga tgtggtaatt tccaaggcaca tatctgtatga ttccatgtgg	60
aatttaacta cctgagtttc ctggacaaag	90

<210> SEQ ID NO 196

<211> LENGTH: 79

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

tggaaaagac aatgatgttt tatttccaag cacatatctg agttgtatgt gtggacagca	60
ctgagactga gtcttcca	79

<210> SEQ ID NO 197

<211> LENGTH: 70

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

ggtgaaaatg atgaattctg gggcgctgat tcatgtgact tgaaaaatgc catccattc	60
ctgattcacc	70

<210> SEQ ID NO 198

<211> LENGTH: 104

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

tggtctcaag gaagggatga tggccaggatt gagactcaag aaaaggatc tgagcctcag	60
agctttgaag gagccacttg gtccctgacc ttccttagagg caaa	104

<210> SEQ ID NO 199

<211> LENGTH: 96

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199

acccctggca gcccctcctg atgattcttc ttccctgagca cgctcatgat gagcaaactg	60
agcctctaag aagttgactg aaggggctgc ttcccc	96

<210> SEQ ID NO 200

<211> LENGTH: 77

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

agtttgccat gatgaaatgc atgttaagtc cgtgtttcag ctgatcagcc tgattaaca	60
catgctctga gcagact	77

<210> SEQ ID NO 201

<211> LENGTH: 86

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

tggcaactgt gatgaaagat ttggctgtat tgtaatagat tttattacta aatgaggaca	60
acagtccctc taaactgtat ttgccca	86

-continued

<210> SEQ ID NO 202
<211> LENGTH: 70
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 202

aagtgaaatg atggcaatca tcttcggga ctgacctgaa atgaagagaa tactcatatgc	60
tgatcacttg	70

<210> SEQ ID NO 203
<211> LENGTH: 217
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203

aagactatac ttccaggat catttctata gtgtgttact agagaagttt ctctgaacgt	60
gttagagcacc gaaaaccacg aggaagagag gtacgtttt ctccctgagcg tgaagccggc	120
tttctggcgt tgcttggctg caactgccgt cagccattga tgatcgttct tctctccgta	180
ttggggagtg agagggagag aacgcggtct gagtggt	217

<210> SEQ ID NO 204
<211> LENGTH: 217
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 204

aagactatac ttccaggat catttctata gtgtgttact agagaagttt ctctgaacgt	60
gttagagcacc gaaaaccacg aggaagagag gtacgtttt ctccctgagcg tgaagccggc	120
tttctggcgt tgcttggctg caactgccgt cagccattga tgatcgttct tctctccgta	180
ttggggagtg agagggagag aacgcggtct gagtggt	217

<210> SEQ ID NO 205
<211> LENGTH: 217
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 205

aagactatac ttccaggat catttctata gtgtgttact agagaagttt ctctgaacgt	60
gttagagcacc gaaaaccacg aggaagagag gtacgtttt ctccctgagcg tgaagccggc	120
tttctggcgt tgcttggctg caactgccgt cagccattga tgatcgttct tctctccgta	180
ttggggagtg agagggagag aacgcggtct gagtggt	217

<210> SEQ ID NO 206
<211> LENGTH: 217
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 206

aagactatac ttccaggat catttctata gtgtgttact agagaagttt ctctgaacgt	60
gttagagcacc gaaaaccacg aggaagagag gtacgtttt ctccctgagcg tgaagccggc	120
tttctggcgt tgcttggctg caactgccgt cagccattga tgatcgttct tctctccgta	180
ttggggagtg agagggagag aacgcggtct gagtggt	217

<210> SEQ ID NO 207

-continued

<211> LENGTH: 217
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 207

```
aaggctatac ttcagggat catttctata gtgtgttact agagaagttt ctttgaacgt      60
gttagagcacc gaaaaccccg aggaagagag gtgcgtttt ctccctgagcg tgaagccgc      120
tttctggcgt tgcttggctg caactgcgtt cagccattga tgatcggttct tctctccgta      180
ttggggagtg agagggagag aacgcgggtct gagttgt                            217
```

<210> SEQ ID NO 208
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 208

```
ggtgtcagatg atgacactgt aaagcgcacca aagtctgaac aaagtgtattt gtacctcgtt      60
gtctgatgca cc                                         72
```

<210> SEQ ID NO 209
<211> LENGTH: 74
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 209

```
gggtgcaaat gatgcataatg ttagcgcacca aagcctgatc tttgctgatt agtctataatt      60
aactgactgc accc                                         74
```

<210> SEQ ID NO 210
<211> LENGTH: 73
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 210

```
gttcagatga tgaatttaac tgttcaactg ctgaatgata acgggcatga actaaaactt      60
aattctgaca gag                                         73
```

<210> SEQ ID NO 211
<211> LENGTH: 71
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 211

```
gatgttatga tgatggcga aatgttcaac tgctctgaag gggctgaatg aaaatggcct      60
ttctgaacat c                                         71
```

<210> SEQ ID NO 212
<211> LENGTH: 97
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 212

```
atgcgatgat gagtgaagta gagcctgacc tggtattgcc attgcttac tggggcctt      60
gaccagggtta tcatcttta atcttctctc tgagctg                            97
```

<210> SEQ ID NO 213
<211> LENGTH: 109
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 213

tcccaatgt gagttgccat gctaatactg agccaccagg tagggcagtg ttgccttgtt	60
ttgggtgcca gtgagttaa caaaaacttct cacatgaaga tctgagggg	109

<210> SEQ ID NO 214

<211> LENGTH: 103

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214

ccctgtat gagttgccat gctaatacgg agacaccagg tagggagttt taccctaact	60
tgggtgttgt tgaaataaac tcttctcgtaatgctgag ggg	103

<210> SEQ ID NO 215

<211> LENGTH: 148

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 215

gtctgtat ggagccatg cgtgtcatct gggctctgg ctcccctgcc agtgcagccc	60
tggcagtgtc ctacttccca gggctgttgt ctgcctggcg ggaaggctct gggcaaagga	120
tcagtctttg tactctgaga gcagacta	148

<210> SEQ ID NO 216

<211> LENGTH: 84

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 216

gtgttcaatg atgatttcta tttgtttgcc tgatttcctt ttggataatg aaggcattt	60
tagtcactac ctcttcgtac acac	84

<210> SEQ ID NO 217

<211> LENGTH: 90

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 217

gcctttgcag ctgtatgtatc agtttttc cccatcgat cgaccctgtt gatcttaca	60
ctattggcca gttttgtctg atgcattggc	90

<210> SEQ ID NO 218

<211> LENGTH: 91

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 218

gctggcatat atgatgactt agtttttc cccgacagat cgactatgtt gatctaactt	60
ttcttaagcca gtttctgtct gatatgccag c	91

<210> SEQ ID NO 219

<211> LENGTH: 79

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 219

tgtaaatgt gacttcactt tttccccat cagatcgaca atgctgacgt ctttatattt	60
---	----

-continued

gccagtttagt tctgataca

79

<210> SEQ ID NO 220
<211> LENGTH: 104
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 220

atcctttgt agttcatgag cgtgatgatt gggtgttcat acgcttgtgt gagatgtgcc	60
acccttgaac ctgttacga cgtgggcaca ttacccgtct gacc	104

<210> SEQ ID NO 221

<211> LENGTH: 126
<212> TYPE: RNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 221

ucacggugau gaaagacugg uuccuuuaaca uucgcaguuu ccacgguagg aguacgcuu	60
cgaaccccauc guuaguacuc ucggugaccg cucuucuuua gagaccuucc uaggaugucu	120
gaguga	126

<210> SEQ ID NO 222

<211> LENGTH: 102
<212> TYPE: RNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 222

gugaaugaug aauuuuauuc uuugguccgu guuuuauugug ggaaguaaga ccccccgaau	60
gagugacaaa agagaugugg uugacauca cagauaucga cg	102

<210> SEQ ID NO 223

<211> LENGTH: 89
<212> TYPE: RNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 223

ucaaaugaug uaauaacaua uuugcuacuu cagauggaac uuugaguucc gaaugagaca	60
uaccaaauua caccaagauc ucugaugaa	89

<210> SEQ ID NO 224

<211> LENGTH: 186
<212> TYPE: RNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 224

aacuauuaca gucgaugagg auagguaua guucaugugu aacaucugug uuuuaaaaaua	60
acucuaguua uccggggcgu uuuucacaaa guuuguguaa gaugcuuucc ugggucgaug	120
uggauugugc cguggcuuu uucaccaccc uuauagcggu gcuuuaacua uuaauaacug	180
aggcug	186

<210> SEQ ID NO 225

<211> LENGTH: 124
<212> TYPE: RNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 225

aggaaguuuu uuccuuuuua uaugaugauu augagugcau uggcucgag uugcuguuug	60
gcuuuuugcca aaucaguaac gguguggaaa aacucaagcu accuuuuuuu acuuuuauucu	120

-continued

gacc	124
<210> SEQ ID NO 226	
<211> LENGTH: 95	
<212> TYPE: RNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 226	
cauaaugaug aaaaaaaaauu uuaaucaaaca guuauccug ucugaauggg uaauaaauagg	60
uaaccucuca uauguugaua uuuguauuuuc ugaua	95
<210> SEQ ID NO 227	
<211> LENGTH: 89	
<212> TYPE: RNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 227	
uuuuuugaug aaaauccaaau guaucccaaau acauauucga cuagucauug acgaugcugu	60
cguaacuuau caccaucuuu cgacugauu	89
<210> SEQ ID NO 228	
<211> LENGTH: 95	
<212> TYPE: RNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 228	
uuuugugaug auacugccga uucuggcauu caaaaaagug acuagcaaaa uugcgauguu	60
gucaacuuua auuacaccau cuuuucggggc ugaua	95
<210> SEQ ID NO 229	
<211> LENGTH: 97	
<212> TYPE: RNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 229	
guaaaaugacg agaaaaaaagc ugugcaccag ucugaacaug gaugccacaa guacucaggu	60
guccuaugaa gcauuuagua uacccaaauu ucugauc	97
<210> SEQ ID NO 230	
<211> LENGTH: 110	
<212> TYPE: RNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 230	
uccccuauga uaaaaaauua uuaaucaau accaaauugu ccgacugaa agugguuuaa	60
ciacaugucg acaacccuuu uucguuaagu uucagccuug uaugaggggu	110
<210> SEQ ID NO 231	
<211> LENGTH: 172	
<212> TYPE: RNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 231	
aaugaccuuuc caaguuuuua aaagaauacg augauauuu uugcguuuca aaucgaacaa	60
uucuucucgg agcgaucuga gguuuuuaug gagauagcg uuccugcgca acccauugau	120
cuuguuacau ucuuuagaau gacaaggacg cuuuuauaaa auucugauuc uu	172
<210> SEQ ID NO 232	

-continued

<211> LENGTH: 99
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 232

auauaaugaug	auauccuaua	acaacaacaa	caugaa <u>uuuc</u> uucguccgaa	uccuuuauag	60
guggaaacaa	acuuugacaa	uagcuuuuua	acacugaua		99

<210> SEQ ID NO 233
<211> LENGTH: 112
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 233

cuaa <u>augaug</u>	auuu <u>ucacuuua</u>	uaccuaua <u>ug</u>	uuuuuu <u>cugg</u>	cauc <u>ucuaau</u>	guuagg <u>gaugu</u>	60
gaaguuuu <u>aag</u>	uacu <u>cuccau</u>	u <u>caa<u>ugaaua</u></u>	cauuuu <u>uuga</u>	caau <u>aucuga</u>	uu	112

<210> SEQ ID NO 234
<211> LENGTH: 89
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 234

uaga <u>augaug</u>	aa <u>agaggua</u> g	cauuu <u>ugcag</u>	cagauuuu <u>uc</u>	gugau <u>ugaa</u> u	caa <u>aca</u> aaaga	60
uuaaccuuua	cagaacc <u>gcu</u>	acacugaua				89

<210> SEQ ID NO 235
<211> LENGTH: 107
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 235

uauuaug <u>aug</u>	auuuuuuu <u>ua</u>	auuc <u>acacug</u>	u <u>acuagauu</u> g	gucu <u>cuuu</u> aa	cgaagg <u>ggcu</u>	60
aa <u>uugaugac</u>	u <u>aca</u> aaa <u>ua</u>	aa <u>aa</u> aa <u>acug</u>	auuu <u>uaugac</u>	ucugaaa		107

<210> SEQ ID NO 236
<211> LENGTH: 92
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 236

uacuaug <u>aug</u>	aa <u>ugacauua</u>	gc <u>gugaacaa</u>	ucu <u>cugaua</u> ac	aaa <u>aucgaa</u> a	gauuuu <u>uagga</u>	60
uuagaaaa <u>ac</u>	uu <u>auguugcc</u>	u <u>uccuuc</u> uga	aa			92

<210> SEQ ID NO 237
<211> LENGTH: 91
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 237

uuug <u>augaug</u>	auu <u>acacucc</u>	aug <u>cuauca</u> u	uga <u>acgugu</u> u	cga <u>ugua</u> aa	u <u>ugaaua</u> cga	60
ugauuu <u>aaaa</u> au	u <u>guuguuu</u> ac	g <u>cuuuc</u> uga	aa			91

<210> SEQ ID NO 238
<211> LENGTH: 86
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 238

uaagaug <u>aug</u>	au <u>caacuuu</u> u	ua <u>uaucua</u> ua	acuuu <u>cguu</u> uc	u <u>acugacug</u> u	gau <u>caaac</u> ga	60
--------------------	---------------------	---------------------	----------------------	---------------------	---------------------	----

-continued

ucuuuguagag aacuuuuuacu cugaau	86
--------------------------------	----

<210> SEQ ID NO 239
<211> LENGTH: 98
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 239

uuauuuugaug aaauagacacc acaaucguu uuuuuuuuauc cggcgaugau uccuuuggaa	60
uaugugccau ggauuacauc augcaucacc aucugauu	98

<210> SEQ ID NO 240
<211> LENGTH: 87
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 240

uaacaugaug aaaaaauuaua uuaacacaga ccuguacuga acuuuucgaa guuuugcaga	60
uaacaaauuu gcuuuuuuuc ucugacu	87

<210> SEQ ID NO 241
<211> LENGTH: 88
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 241

aagcgugauu auaaaaaaug auuuuauau uuuucugagg aaguauaung aggacauauu	60
gugaauuagg aauucuucgu uuaugauc	88

<210> SEQ ID NO 242
<211> LENGTH: 96
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 242

cuuuuugaug auauucuuua cgaacuuuuu gacguuagac uucugaagga gauuagaccc	60
uccuauggaa gagaaacucg uuaaacuuau cugagu	96

<210> SEQ ID NO 243
<211> LENGTH: 78
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 243

cuuuaugaug aaaacuauuc cuuauucucg acuagucuuu gacaaugcug ucguuuuauc	60
accaucuuuc ggcugacu	78

<210> SEQ ID NO 244
<211> LENGTH: 103
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 244

guuaugaug auaaccaaag augcauaguu caacugauug aacauacuau cgaaaugaaag	60
auaaaaauuu ccaucgaaau uagucuuucg cuccuaucug aac	103

<210> SEQ ID NO 245
<211> LENGTH: 89
<212> TYPE: RNA

US 9,273,294 B2

105

-continued

106

<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 245

uacaaugaug	auaaaauuua	cuauucaguu	cugcuucuga	acccaaaauaa	uaggaagaua	60
accaauuuua	ccaaagcuca	aaucugauu				89

<210> SEQ ID NO 246

<211> LENGTH: 100

<212> TYPE: RNA

<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 246

uuuuuauaug	auuuuauguu	uucaaauuuu	ucuacauuuu	cugaauuuuu	agcuaacaau	60
aguuaauaau	gaagauauac	gacuaauaac	aauucugaaa			100

<210> SEQ ID NO 247

<211> LENGTH: 255

<212> TYPE: RNA

<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 247

uuuaauaug	aaguuuuuaa	uuuuccguug	gucuauuaag	aacagaagua	cuucaaaacu	60
acuuuuuuuag	accauccuuu	uacaguauuu	uuucaaauuu	guaaaacuuuc	ucauuuucuu	120
ugugucuuua	ugaucucauc	guuucuggugg	accuaauaca	gacgcacgg	auacuucguu	180
ucuguuggag	aaauuuggga	gucuuuuuaau	gugaugagug	gccaacauaa	ccuuauaguc	240
auaguuuacac	ugauu					255

<210> SEQ ID NO 248

<211> LENGTH: 101

<212> TYPE: RNA

<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 248

uuguaugaug	aggaaccaga	uagggacaac	agauucucaa	gugacgagga	acaucuuua	60
aagcccaguu	uuuaguagag	cuuagggcgc	cuuuacugac	u		101

<210> SEQ ID NO 249

<211> LENGTH: 100

<212> TYPE: RNA

<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 249

aaaaauaug	auuuuuuuua	acacaauuu	ugcuagauag	uaucugaaag	cäucaaacu	60
uuaugauuac	aguguuuucg	acaguuuuua	aucucugaac			100

<210> SEQ ID NO 250

<211> LENGTH: 85

<212> TYPE: RNA

<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 250

ucaaaugaug	aaauaccaau	gcaacagagu	caagcucuga	guuucaaaaa	gaaacaugga	60
cgagauugcu	uuuuuauuac	ugacc				85

<210> SEQ ID NO 251

<211> LENGTH: 82

<212> TYPE: RNA

<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 251

```
uaaacauaug acuaaguugu cgccccaaagc ggaucuuuga aaugacugau uuuacaaaca      60
acaaaacacug aaaaauucuga aa                                         82
```

<210> SEQ ID NO 252
<211> LENGTH: 136
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 252

```
uaucauaug agcauuuuuu uuacugcggu aucguauuga cgggggcugu uuaaguacag      60
ucuguuuuau aaucuauuu cauuuauuu uuauauuuuc uaccgaggaa auugacucuu      120
aacagauuuug cugaaaa                                         136
```

<210> SEQ ID NO 253
<211> LENGTH: 101
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 253

```
guuuuauaug agaccacguc cuuagugaca augcuauaaa cccagcucuu cgauucguuu      60
uuaauugaaag ggagaagauu uuuuugucaa acgcucugag u                                         101
```

<210> SEQ ID NO 254
<211> LENGTH: 164
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 254

```
ugauauaug auuuguuguc gaccgggggg acauauuagu aucguuuaaa gggucgcgu      60
cuacucucau cguucuuuuug uguacaaauu uuuuuaaggaa gcgauguuga uggcauuuug      120
guuucuuuagu ggagaauuuga ugauugguca caagacauu gauu                                         164
```

<210> SEQ ID NO 255
<211> LENGTH: 89
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 255

```
uuauauaug auaaccuuuuc cagcucacuc agaucuuuug auaugauuuga uaaaaauuuc      60
cuauccaaca uucaucaauu uaucugacc                                         89
```

<210> SEQ ID NO 256
<211> LENGTH: 91
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 256

```
ugaugugau gacaacuuuuc gagcuauuaa uuuucuugag aacaucuau aagaaaaacgu      60
cucaucaaaau gauuugcact ucagucugau c                                         91
```

<210> SEQ ID NO 257
<211> LENGTH: 103
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 257

-continued

<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 264

guaacugaaau	gaugauauaa	uuugcgaucu	agggcuaauc	acuuggaaaca	ccgccauguu	60
cuauaugggu	gauuagcgaa	gugcgaaaaa	uuuuuuaucu	gauuuuuuc		109

<210> SEQ ID NO 265
<211> LENGTH: 190
<212> TYPE: RNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 265

ggcccugaug	auaauggugu	cucuuuuuuc	cucguccgau	ucgaccauga	cgacaaggga	60
uuuuuaucug	uucucuuuaau	gcgaaugauu	uugaaaagau	guugcuiucug	ugacauuuuu	120
uuuuuaaucau	uuguguuuugc	aaacgggaac	uuuuuugcc	aguguuauc	aacacaugca	180
gaucugagcc						190

<210> SEQ ID NO 266
<211> LENGTH: 451
<212> TYPE: DNA
<213> ORGANISM: *Homo sapiens*

<400> SEQUENCE: 266

gggttgcgga	gggtgggct	gggaggggtg	gtggccattt	tttgtctaac	cctaactgag	60
aagggegtag	gcgcgtgtct	tttgcgtccc	gwgctgtgtt	tttcgtcgctg	actttcagcg	120
ggcggaaaag	cctcggcctg	ccgccttcca	ccgttcattt	tagagcaaac	aaaaaatgtc	180
agctgctggc	ccgttcgccc	ctccccggga	cctgcggcgg	gtgcctgcc	cagccccgga	240
accccgctg	gaggccgcgg	tccggccggg	gtttctccgg	aggcacccac	tgccaccgcg	300
aagagttggg	ctctgtcagc	cgcggtcttc	tccggggcga	ggcgaggtt	caggctttc	360
aggccgcagg	aagaggaacg	gagcgagtcc	ccgcgcgcgg	cgcgattccc	tgagctgtgg	420
gacgtgcacc	caggactcgg	ctcacacatg	c			451

<210> SEQ ID NO 267
<211> LENGTH: 547
<212> TYPE: DNA
<213> ORGANISM: *Oryctolagus cuniculus*

<400> SEQUENCE: 267

ttggaaaacc	tcgcgatagc	cggggacgct	cgccctcggc	caatccgcgc	gwgagcgcc	60
gtcccttta	taagacgact	ccggccggcg	cgcgccgggc	tgaggagggt	gggctcgga	120
ggggccccgt	catttctcat	ctaaccctaa	ctgagcagg	cgtaggcgcc	gwgctttgt	180
ttcccccgc	gctgttttc	tcgcgtactt	tcagcgcgtg	ggaaaagcct	tggcttaccg	240
ccgtccacccg	tccatttcgc	agtaaacaaa	aaatgtcagc	cgctggccgg	tccgccttc	300
ccggggacct	gcgggtggctc	gcccggccgg	ccccgtgcc	ccgcctgagg	ccgcggcgg	360
ccggggacct	ctccggaggt	gcccataatgc	ccgcgcaaga	gttaggctct	gtcagccgcg	420
ggtccctcgg	gggccaagg	cgaggcgcag	gccgtctggc	cgcaggagaa	ggaacggagc	480
gggtccccc	gcgtgggtgcg	cttccctgag	ctgtggact	tgcacccggg	actcggctca	540
aacacgc						547

<210> SEQ ID NO 268

-continued

<211> LENGTH: 517
<212> TYPE: DNA
<213> ORGANISM: Cavia porcellus
<400> SEQUENCE: 268

```
cctgagactc agtctcgca cagccgtggc aggcgtcagc caatccgcgc gggcgccgac      60
cactgtttta taaggagcct ctgcgagccg ctggggccggg aggggtggg gtcttcctg      120
tctaacccta aggtgaagag gacgtgggtg cegtgtttt cgctcccgca cgctgtttt      180
ctcgctgact ttcagcgtgc agaaaagcct tggcctaccg tcggttatg tctaattaga      240
agcaaacaaa aaatgtcagc gtggccgggc cgccccctcc ggataacctgc ggccgctcgt      300
ccacccggccc ccgagccccc cctaggccgc ggccggcgcg gggcttcct ggaggccccc      360
atggccggccg cgaagagtcc gtctctgtca gctgcgggtc gcccgggggc cgccggagag      420
tcccaggcct tggccgcagg gagagaaacg gacgagggtcc tcgcgcgggtg cactccctg      480
agctgtggga agtgcaccgg gacgggctcc tacaagg                                517
```

<210> SEQ ID NO 269
<211> LENGTH: 476
<212> TYPE: DNA
<213> ORGANISM: Cricetulus griseus
<400> SEQUENCE: 269

```
gcgcgcgaga gttcgagctc cagcgagac cggcgccggc caatcagcgc ggccacccc      60
gggtacttaa gggcgacctg gcggggcggt gccagtcataa ccctgaattc tgagagctgt      120
gggtactgtg ctttcgtctc cgccccgtgt ttttctcgct gacttccagc gggcgggaaa      180
gtccagacct gcagcgggcc atcgcgcgtt ttccaccaca aaaaaatgtc agcgtggc      240
tcatgtgcct ggagccttgc ggccggccgc ccagcccccgc acccgctga ggccgcggtc      300
ggcctggagt ctcgggctc cgctgcccgc gcaagagct agactctgtc agccgcgggg      360
cgtcaggggc tggggcgagc cccggcagcg ccgcaagcag agaaacggag ctggtccctg      420
gaacggtgac ttccctgagt tgtggaaat gcaccaggaa ctgggttccc acaacc      476
```

<210> SEQ ID NO 270
<211> LENGTH: 397
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<400> SEQUENCE: 270

```
accttaaccct gatttcatt agctgtgggt tctggtttt tgttctccgc ccgtgtttt      60
tctcgctgac ttccagcggt ccaggaaagt ccagacctgc agcggccac cgccgcgtcc      120
cgagcctcaa aaacaaacgt cagcgccgaa gctccaggtt cgccgggagc tccgcggcgc      180
cgccggccccc agtcccgtaa ccgcctacag gccgcggcccg gctgggggtc ttaggactcc      240
gtgcgcggccg cgaagagctc gcctctgtca gccgcggggc gccggggggt ggggcaggc      300
cgccgcggccg ccgcgaggac aggaatggaa ctggtccccg tggtgggtg cttacctgag      360
ctgtgggaag tgcaccggaa actcggttct cacaacc                                397
```

<210> SEQ ID NO 271
<211> LENGTH: 388
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus
<400> SEQUENCE: 271

```
gtcttaaccct attgttatag ctgtgggttc tgttcttttgc ttctccgc gctgttttc      60
```

tcgctgactt tcagcgggcc tggaaagttc agacctgcag cgggtcacgg cgcatctgg	120
aacctcaaaa aatgtcagcg taggagctct ggtgccagag ctccggggcg ctggggcc	180
cagccccgta cccgcctgga ggccgcggac ggctggggctt cttagaactc cgctggcc	240
gtgaagagct agtctctgtt agtacgggg caccgggcgc tggggtcagg ccgggagagc	300
gcccgaagga cagtaacgga actggtcctt gagttcggtg gtttcctga gatgtggaa	360
gtgcacctgg aactcagttc ctacaacc	388

<210> SEQ ID NO 272

<211> LENGTH: 544

<212> TYPE: DNA

<213> ORGANISM: Felis catus

<400> SEQUENCE: 272

gaggacggat ctcgcgagaa ccgtgacggg agggcttaag ccaatcgccg cgtacggccg	60
ccgctgtctt tataggagc cgcggcggtt tgcacctcggtt gttgtggagg gtggggctgg	120
gaggggaagc ggtcagtttt tgcataaccc taactgagaa gggcgtaggc gccggcgctt	180
tgtttcccgc acgtgttttt ttctcgatc ttccagcggtt cggaaaagcc tggcgttacc	240
gcgcgtccacc gtacagttt gacaaacaa aaaatgtcag ctgctgactt gtcggccct	300
cccgaggacc tcgcggggct cgcctcccta gcccccggtt cccgcctaga ggccgcggc	360
ggcccgccggc ttctccggag gcacccattt cgcgtcgaa gagttgggtt ctgtcagccg	420
cggttcctt gggggggccg agggcgaggc tctgaccgc gggagagaaa cgggagccagg	480
tcccccgccg cggtgccgtt ccctgagctg tggacttgc acccggaact gggctcagac	540
acat	544

<210> SEQ ID NO 273

<211> LENGTH: 443

<212> TYPE: DNA

<213> ORGANISM: Bos taurus

<400> SEQUENCE: 273

gggttgcgga ggggtggccc cgggttgggtt gcagccattt ctcatctaac cctaatttag	60
acagggtag ggcgtgtgtt tttggttacc ggcgcgtgtt tttctcgctg actttcagcg	120
ggcgaaaaag cctcgcccta cgcgcateca ccatccagtc tgcaacaac aaaaaatgtc	180
agccgtgtgc tcgctcacct ctcggggaa cctgcgggtt tccggccgc cagccccagt	240
gccccgcctg aggccgcgtt cggcccggtt cttctccggaa ggtgtccatt gccgcgtga	300
agagttgggc tctgtcagcc gcgggtcgct cgggtggccg aggcatggct gtaaccgcag	360
ggaaaggaaac ggagtgggtt cccgcgcgc ggtgcgttcc cctgagctgtt gggacttgca	420
cccgggactc ggctcagaca tcc	443

<210> SEQ ID NO 274

<211> LENGTH: 482

<212> TYPE: DNA

<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 274

gagagctgcc ttattctgaa ttccaaaaat gttcagtaaa ttatgtctt aacaggagct	60
gttttcacctt attaaaagat gttatcaggc gggttgcaga gggcaggccg ggagaggagt	120
ggccatccccaaaatctgac cctaaactgaa acagggttagt gcaactgcact tttgtttcc	180

-continued

cgagcgctgt ttttcttgct gactttcagc ggatggaaga gccaccatcc agtctgaaac	240
aaacaaaaaa tgtcagccac tggctcggtc actgctcccc ggaacctaaag agtctcgccc	300
gcccaagcccc ccgcttctcc caaaggccc actgcctccg cgaagagtgg ggctgtgtca	360
gccgcgggtt ttcggggcc aaggcgaggc tctgaccgca gggaaaggaa gagttcccta	420
agctgtggca tgtcagcca ggacttggct cagatacttg caaagaaaaa aaaaaaaacc	480
cc	482

<210> SEQ ID NO 275

<211> LENGTH: 540

<212> TYPE: DNA

<213> ORGANISM: Equus caballus

<400> SEQUENCE: 275

gaggggcggct ctcgcgatag ctccggcagg cgggcctcg ccaatggcg cgccggcg	60
tgcctccctt ataaggaggt gcccggcaggc acggcgccggg tgggggagag tgggtctgg	120
cggggcggcg gtcacgtttt gtctaaccct aactgagctg ggccggaggcg ccgcgtttt	180
gtctcccccg cgctgtttt ctcgtgact tttagcgggc ggaaaagcct cggcttaccc	240
ccacttacca tccagtctgg agtaaacaaa aaatgtcagc cgctggctcg ctgcaccctc	300
ccgggaccct gcgacggctc gcccggccag ccccccgc cccgcctggag gcccggctcg	360
gccccgggct tctccggagg cgcccaatgc cgccgcgaag agttgggc tgcagccgc	420
gggtgcctcg gggggccaggg acggggctct ggccgcagg agaggaacgg agcgggtccc	480
cgcgcgcggc ggcgttccct gagctgtggg acgtgcaccc gggactcggc tcaaacaacgt	540

<210> SEQ ID NO 276

<211> LENGTH: 549

<212> TYPE: DNA

<213> ORGANISM: Elephas maximus

<400> SEQUENCE: 276

ggtcagetc tcgcgagagc cagtgggaga aggccctggc caatccgc ggtggcggtc	60
tctccctta taaagagggtg cggcgccgcg gctggtgccg tgggttgagg agggtaacgcc	120
cgggagggcg gtggctgtt ctgttctaac cctaactgat aaggcgtag gcgcgtgt	180
tttgttcccc gcgcgttgtt ttctcgctg actttcagcg ggccggaaaa gcctcggtct	240
accgcgtct accgatagcc tggagcaac aaaaaatgt cagccgcgg ccgcgtcccc	300
ctcccgggaa octgcgttgtt ctgcggcc cagccccgtt cccgcgttgg agggccgcgt	360
cgccctgggg ttctccgga gttcccgctt gcccgcgaga agagttggc tctgtcagcc	420
gggggtcccg cgggaaccaa gggcgaggctt gggccctctt gaacgcagg agagaaacgg	480
agcggttccc cgcgtgcgtt cgcgttccctg agttgtggg tgcgcgtcg gggctcagct	540
ccgacaggt	549

<210> SEQ ID NO 277

<211> LENGTH: 465

<212> TYPE: DNA

<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 277

acgcgtggcg ggtggaaaggc tccgcgtgtc ctaaccctaa tgggggaaat tgatgggtct	60
gtcgccgcgc tccctccgcg cggccgcgtt ttactcgct gactttcagc gggcgagg	120
agccgcggccg ggggggaggc gggcgccggg agggggccgg ggcgcggcgg cggtgggggt	180

-continued

cgggggggggg agagaaaaggg ccgaaagggg ctccgcggcc aaaaaaacgt cagcgagggg 240
 tccgcgtcgcc cccatcgcc ctggggtccc cgctcgctg gccgcggctcg gccggcaccc 300
 gccattgcgg cccgcaagag ttgcctctg tcagcctcg ggccgcggc gaggtgcggc 360
 gcccggcccc cccgcggccag cagagcaaac gggagcggcg ccccccgggt aaccccccgcg 420
 ctccccctgcg ccgtggggcg cccggacggc gtcgctccca cacgc 465

<210> SEQ ID NO 278

<211> LENGTH: 520

<212> TYPE: DNA

<213> ORGANISM: Bufo japonicus

<400> SEQUENCE: 278

gaacgcacgc otacgggtag cagtaagggt agaccgataa ccaatcaaat ggtaatacat 60
 acattacgta attttatgtt taaatacgta tgtttttta ccggtagttt aatttagaggg 120
 attggaaagggt tccgctttagt ctaaccctaa tattgggggt ctgttggaaa cctctttaag 180
 atatgcgtgt tgtttattt gctgactttc agcgccgttccatt gagaggagtt gctgcggcagg 240
 actaaaaaaat gtcagctggg agtcccttccct ctcctttttt tctgcctcac aacctggact 300
 ctttatttag ccgtgcggcca ttgtcgagg ccgcagtcag tttgttctt atacgctgct 360
 gtgcgaaga gttcgctctt gtcagccctcc ggggcaacgc cttgaatttg gagagcctgg 420
 gaatgttaca aagggttaggg aaaataacga gagctgagtt ggcttctccct gtgcgttcc 480
 tgagctgtgg aacttgcatt cccggacggc tctgacactt 520

<210> SEQ ID NO 279

<211> LENGTH: 584

<212> TYPE: DNA

<213> ORGANISM: Xenopus laevis

<400> SEQUENCE: 279

tgcggcaagggt tacagagcgc gccccttaa cccggaaagaa ccaatcgact ccctcgaaatt 60
 gacaggattt cattggctgg aataaaatgtt gccggaaatcg gcagctactt ttttagccagc 120
 gtcggaaagt ctttgaatca gcgtttaag ctcaatgtgg acggaggctct ctgtttcgct 180
 aaccctaata cactggcttc agggcgttgg ctcttcggg cgggtgectgt tgtttactt 240
 gctgactttc agcgccgcacg gagagcaagc gtagacgacg actaaaaaac gtcagctggg 300
 agactccctcc gttcgacacag cccgacactgc tccattgccc aagagcccg gttttctct 360
 gtggaaatgtt tcaaggcgctc cccggctgtt ctgtctgggg ccgcggctgg catcatctgc 420
 tgtcgcgaag agttcgcttc tgtagccct tggggggccct ggtgcggagtt ggagagtcg 480
 ggtctgggg gtcggggagaa caaaagggggg cccggctgggctt ctcaggctca gtcatgtttt 540
 cccttagttt tggatatgc gtgttcagcc agtccccgac atgt 584

<210> SEQ ID NO 280

<211> LENGTH: 317

<212> TYPE: DNA

<213> ORGANISM: Danio rerio

<400> SEQUENCE: 280

gcagagttact ttctctaacc ctaacgcttc tttgcttccct gtacggcttg tatgtgtttt 60
 tgcgtttaacc ttccatcgata ttacatgttgg ctttccgggg tttcgataact ttaaaaaagc 120
 tataagatgtt tctggcgctc ggttccacag gtttggctgt ttgtacgcgg acagtttgc 180

-continued

```
tgccgcggcaag agttcgccgtc tgctgcacat tcggcagggtc tgtggactgc acaacactga 240  
gcagattaac tttagccatgg cgaagggttg cggacacctaa acactgatcc tgcaaatacg 300  
ccaccgcgtca gacatgc 317
```

<210> SEQ ID NO 281
<211> LENGTH: 1413
<212> TYPE: DNA
<213> ORGANISM: *Schizosaccharomyces pombe*

<400> SEQUENCE: 281

aacgcacgc ccatgtcttag aagggtgaca agggaaaatta atcaaacggc tcttgagggc
tttgtgattt atttggaaagt ttgaaggaaa tgattcatag gcttaagta tagtttgcta 1200
ttccaaaacc tgtatactgt ctactagaaa gaacgagtag tctgtttagc ttttcagttt
gtctggatag ttgtttcga tggatttcga attcctgtac tgcttcgtgt aaccgtactc 1800
ttcaactttt cagcattgac aaattattct ttttagctt ttttagagtt ttgatcatta
ggaaatattca taagagaggc tcttcatttgc atcggttgc acgttgcggaa aacatagatc
attccttaccc cttttattat ggctgcagac ttctatcttgc tttttagtttgc 3600
aggcctggac atcaattgaa tcgctgggtt cagtgtaacgt gatgttttgc cttttaaat
tcatttacag tttaatccca cctttcatttgc gtataaaatc tttttagtttgc 4200
ttgtcagatc acaacgaatt tttggtagaa gagtctcggtt tttttagtttgc 6000
aaaatcaagc aatgaagaaa gtttataga tagtttcaat tccccatataca aatattaaat
tgtattggta acaatttttgc ttgtgttgc tttttagtttgc 6600
gtttttttgc tttttagtttgc 7200
aaaaatgact tttttagtttgc 7800
ccgtgttgc tttttagtttgc 8400
tgcgttgc tttttagtttgc 9000
tgcgttgc tttttagtttgc 9600
cttggattct ttgttgc tttttagtttgc 10200
ggtaagatc tttttagtttgc 10800
gttttttagtttgc 11400
tgcgttgc tttttagtttgc 12000
tttttttagtttgc 12600
cagaatttgc tttttagtttgc 13200
ccgttttgc tttttagtttgc 13800
taatgttattt atttgcgttac taqaqqaqat qaa 1413

<210> SEQ ID NO 282
<211> LENGTH: 1301
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 282

aataaaaacta gagaggaaga taggtacctt atgaaaatgt caatggctgt tgcgttgct	60
taatcgatt ttttttttt tcagtcgtg tttttgtac attctacgtt tgagtttcc	120
atcatgcagg cctcagaaat ttggtaggca ctgcgtggta aagagatagt gtcggattc	180
ggattgatct ttcagttgat agcctgctgc tctttcttt tccaaagaat ttcgagtatg	240
ctggtgtcag tgtatgtct tgggtgtcgca aatgtgtgg ttttttattt tgtttctact	300

-continued

tatagatggc taaaatctga gtttagaaaa tgcaaaccgt aaattcttaa acactgctat 360
 tgcattttagt tgctaaagca gtgttttga acttattccct gtttattccctt ctgcgtacgg 420
 atccctttctt cgacctaacc tttaattac catgggaagc ctaccatcac cacaccacaa 480
 cacaatgtt acagctaatt gttttagtc aaagtttgca cgagttcgct gtttatttt 540
 ttctcgttt cttataccta gtatTTTTC tgacactgtt taaggtgaca gaaaaaaagg 600
 agtttaagt agatttgc当地 acagacgggtg ctaagcgctg tcactttatg tctatcttat 660
 cgtaactct ggaaaaagaa aaaggaaaaaa gaacgtcagg gaacatgagt atatatagaa 720
 atggTTTATT ctagttttt ccgtttttc agtagattt tgcctttaaa agaataaatc 780
 ccactacaaa aaggtaaaat aaaaatcta ttcaactgaac ttactgtatga aatttccaaa 840
 tgcgtccccgt acatcgacg atgtgacaga gaaaaatacg agtaggtaaa taagccaaaa 900
 ggcaagggtg tcctttctta agcatcggtt aggttgcgg gcgcgtcactgaaact 960
 gacacaagat caagaacgta atttgagatt ttcaagatg gtttttttag gtatctatta 1020
 aaactacttt gatgatcaat acggattttt tgtcgattt tttccaagc ggaaggaacc 1080
 gtgtgttcat tttatgatc ttgggttgtt attcacagct acttctctta atgccttcga 1140
 tgcatttaga taatTTTGG aaacatTTT tttttgtat tatatTTT gtattgtaga 1200
 aatcgegcgt actgtacttg tatatcgctt tataagcgctt tttaattgtat tgcgtatgac 1260
 gaggataggc ggataggcgg aggtatgcctt cttatattt a 1301

<210> SEQ ID NO 283

<211> LENGTH: 1190

<212> TYPE: DNA

<213> ORGANISM: *Saccharomyces pastorianus*

<400> SEQUENCE: 283

gagaggaagg tggtaaccta ataacacgtc agcgactggg atgtttgcctt gcccTTTTT 60
 aatttgcctt tcaatgtattt tttccattt gagtttctg ttgataagcc tcagagttt 120
 ggtagggccc tagtgggtggc acgggtggc cggaaatcgcc attgagatgt gatgttagtg 180
 ggccattgtg catctttttt atatTTTGGG caatgcgagc acgctagtgc cagtagcgc 240
 ggTTTCTGTT CTTAACGTAC TTATAGATCG CTACGTTATT TCATTTTGAA aatctgagc 300
 ccggggagtg cggatccata catacatgta atttgggtt gcagtttgc tagagtacat 360
 ttttctccgc gattgtctgt cttctttaca ccagttctgt tttccgtctc aacctctca 420
 ttattatggc aagcatctac cattaccaca cccacacacg aacgttaagg ctaatcgta 480
 ttatTTGGA aatTTGTTTCTGTT TTTTTCAAT GTTTCCGTCTC GCTTTCCAAG 540
 tgacagaaaa aaaggagttt gaatttaggtc tgaaaaggc gcaatataa tgataactgtc 600
 acccttaatg tctgatTTTCTGTT CGTCAACTCT GTAAAGGAAA CAAGAGAGAG AAAGGTTGGT 660
 ggagatTTAA TCTGTAGAAA gaggaaggTTTCTGTT ATTCCATTTC TCAAGTAGATT 720
 tttgcTTTTT ACTAGAATTAA ATTAAACCAA TATAAAAGGT TCAAGGAAAA ATCTATTCA 780
 tgaacttattt agaaaacctc aaatgtgtt gatgcattga aaagattaac caaaaaaaaaa 840
 aaggcacgca agcaggtaa aagacttagga ctcccttcgt ttccttccc atttgcctc 900
 aagcatcgaa taagttgc当地 agcaaaacat aaccggccaa atgttacaag agaaaataaca 960
 tgatTTGGG TCTTCTGGC TGGATTGTT TACATATTTC TTACTCATT TTTGAGGAT 1020
 caataacaata ttcttgccc atccttgcta aagtaaagaa cgggcattaa tttccgaaca 1080

-continued

gaaagaattt tttgttcaact ttatggtttt cgcattgtac ttttcctact tgcattagca 1140
 gttgtttggc tcactacttt tttagatgtcacgaataat ttttggacc 1190

 <210> SEQ ID NO 284
 <211> LENGTH: 1544
 <212> TYPE: DNA
 <213> ORGANISM: Candida albicans

 <400> SEQUENCE: 284

 gtagccattt attattctaa cccatattca atgctcttgg agtgtgaata tactcggtac 60
 atgctatttc attaaaggca ttacttcttt tcgttaccat aatcaactaac agtttatttg 120
 tttatgtgg ttaagacaag tacatgtcca gaatataata aataaccgt tgaaaacccc 180
 aggggtctag tgaatcatct gaaagaagca tggctttat tgatagtgtatctttaaat 240
 tgagacctac ttcatgtaca ccaagaagtt agacatccgt acatcaaatac aatgtcttga 300
 cattgagttt actcccccata ttttggaa aagaattgtt ctccataat ttgtatgata 360
 ctttggag cacaaggcgc atagtccttt gcttcgcca tcacaaatgt tgcataatcca 420
 agaatgcaaa tgattgtttt tcaaaaggaa attaaaaacc aagatattgt taatgggaaa 480
 gaaaatttca tgtttattat ttgcaatcat tagtcattcc ggccgattac ttcatcttag 540
 tcactgcattt gtttattat ctactttggaa ggtacttctt ttcattggag ttcaacaacc 600
 cccattttccca tgcttctttt ttgggttattt gtgattttttt ttagtttga aggaaattaa 660
 aatatattatc aaacaaaaat agggtagagg ttcccttttta tgatgagaaa ctgaaatgg 720
 atgttgggtt ttgggtgaaa ttatgttttag caggtgtttt ataatgggtt aactggagag 780
 ccaatgtgga aattgatctg aggtttcaaa aactgggggtt gtttttttt tcaactaaag 840
 tgcgcattcc aagtatctc atctatctgt tgacacattc tctttctgt gcgttttgt 900
 cagataaaag gtttaccatt cacttgcgt aagttttttt gatactggaa atgcaaccct 960
 ctttcattgc actgtctcggtt cggccctctgt ccctgcttta agaattccaa cggctgtgt 1020
 aaaagagtca ctctatcaat tgcattgtt ttctcatatg agtttccaaa atttgcga 1080
 gatgggggtt tatgttattt agaaaacttt tctttccaa tccagtcaac tcttttgat 1140
 gggcattgtt tgggtcataa aagtgtgagt taaattgtgt tgaataaaat cactagccat 1200
 gtttcttgg ggttactgggtt ggatccccc tgggttacttg tgggtttagt gatccat 1260
 ctaaggcattt cccgaattgtt ggatagtttcaaaactcgaa aaaattggaa gttaggtatg 1320
 ttgggtgtga aacagatagc attacgtat tgcaggtaaa gtggttcaca atttgcattt 1380
 tcgcgcgtggaa ttggatgtgaa gaagctctgg agtacgagttt ttagtacatac agcatagtt 1440
 ctgttggaaa ggttacatttgc cacaagaaga atgttggatgtt gtaatgtgtt ttatgat 1500
 agttggattt ggttgcattcc ttcttattttt tttttttttt ttct 1544

<210> SEQ ID NO 285
 <211> LENGTH: 17
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (13)..(13)
 <223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 285

acattttttg ttnctga

-continued

```

<210> SEQ ID NO 286
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 286

```

```
gacatttttt gtntctga
```

17

```

<210> SEQ ID NO 287
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 287

```

```
tgcacatttt tgnctga
```

17

```

<210> SEQ ID NO 288
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 288

```

```
ctgacatttt ttntctga
```

17

```

<210> SEQ ID NO 289
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 289

```

```
gctgacattt ttntctga
```

17

```

<210> SEQ ID NO 290
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 290

```

```
agctgacattt ttntctga
```

17

```

<210> SEQ ID NO 291
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

```

-continued

<400> SEQUENCE: 291

cagctgacat ttntctga

17

<210> SEQ ID NO 292
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 292

gcagctgaca ttntctga

17

<210> SEQ ID NO 293
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 293

tgcaagctgac atnctga

17

<210> SEQ ID NO 294
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 294

ctgcagctga canctga

17

<210> SEQ ID NO 295
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 295

cctgcagctg acnctga

17

<210> SEQ ID NO 296
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 296

gcctgcagct ganctga

17

<210> SEQ ID NO 297
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 297

ggcctgcagc tgnctga

17

<210> SEQ ID NO 298
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 298

gggcctgcag ctnctga

17

<210> SEQ ID NO 299
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 299

cgggcctgca gcnctga

17

<210> SEQ ID NO 300
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 300

acattttttg tt

12

<210> SEQ ID NO 301
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 301

gacattttt gt

12

<210> SEQ ID NO 302
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 302

tgacatttt tg

12

<210> SEQ ID NO 303
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 303

ctgacatttt tt

12

<210> SEQ ID NO 304

-continued

```

<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 304
gctgacat tt                                12

<210> SEQ ID NO 305
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 305
agctgacatt tt                               12

<210> SEQ ID NO 306
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 306
cagctgacat tt                                12

<210> SEQ ID NO 307
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 307
gcagctgaca tt                                12

<210> SEQ ID NO 308
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 308
tgcagctgac at                                12

<210> SEQ ID NO 309
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 309
ctgcagctga ca                                12

<210> SEQ ID NO 310
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 310
cctgcagctg ac                                12

<210> SEQ ID NO 311
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 311
gcctgcagct ga                                12

```

-continued

<210> SEQ ID NO 312	
<211> LENGTH: 12	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 312	
ggcctgcagc tg	12
<210> SEQ ID NO 313	
<211> LENGTH: 12	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 313	
gggcctgcag ct	12
<210> SEQ ID NO 314	
<211> LENGTH: 12	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 314	
cgggcctgca gc	12
<210> SEQ ID NO 315	
<211> LENGTH: 65	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 315	
aataagtgtat gaaaaaaagc tgacattttg atgatggcca gtgataacaa cattttctg	60
atgttt	65
<210> SEQ ID NO 316	
<211> LENGTH: 65	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 316	
aataagtgtat gaaaaaacct gcagctgacg atgatggcca gtgataacaa cattttctg	60
atgttt	65
<210> SEQ ID NO 317	
<211> LENGTH: 94	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 317	
cagcctgaaa ttagtacttctttaaaaaatt agctgacatt ttctgacat ttctctgg	60
acacagtttt tgccttatga atctgatcag gctg	94
<210> SEQ ID NO 318	
<211> LENGTH: 94	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 318	
cagcctgaaa ttagtacttctttaaaaaatt cctgcagctg actctgacat ttctctgg	60
acacagtttt tgccttatga atctgatcag gctg	94
<210> SEQ ID NO 319	

-continued

```

<211> LENGTH: 70
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 319
aaagttagtg atgaatagtt ctgtggcata tgaatcatta attttgcatag ctgacattt      60
tctgaagtcc                                         70

<210> SEQ ID NO 320
<211> LENGTH: 70
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 320
aaagttagtg atgaatagtt ctgtggcata tgaatcatta attttgcatcc tgcagctgac      60
tctgaagtcc                                         70

<210> SEQ ID NO 321
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 321
aatagatttt ttntctga                                         17

<210> SEQ ID NO 322
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 322
gaatagattt ttntctga                                         17

<210> SEQ ID NO 323
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 323
tgaatagatt ttntctga                                         17

<210> SEQ ID NO 324
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 324
cagtgaatag atnctga                                         17

```

139

-continued

<210> SEQ ID NO 325
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 325

tcagtgaata ganctga

17

<210> SEQ ID NO 326
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 326

ttcagtgaat agnctga

17

<210> SEQ ID NO 327
<211> LENGTH: 65
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 327

tttttatttc tttctaagtg ggtactggca ggagtcgggg cctagtttag agagaagtag

60

actca

65

<210> SEQ ID NO 328
<211> LENGTH: 55
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 328

agtaatcctt cttacattgt atcgtagegc tgcatatata atgcgtaaaa ttttc

55

<210> SEQ ID NO 329
<211> LENGTH: 55
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 329

agtaatcctt cttacattgt atcgtagegc tgcatatata atgcgtaaaa ttttc

55

<210> SEQ ID NO 330
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 330

aacgtccttc tactattgga a

21

<210> SEQ ID NO 331
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 331

ttctctgtca catcggtcga tgtac

25

140

-continued

<210> SEQ ID NO 332	
<211> LENGTH: 21	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 332	
aacgtccttc tactatttggaa a	21
<210> SEQ ID NO 333	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 333	
tttctgtca catcggtcgaa tgtac	25
<210> SEQ ID NO 334	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 334	
tcaatccgaa atccgacact atctc	25
<210> SEQ ID NO 335	
<211> LENGTH: 32	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 335	
gaaaatttcat cagtaaggttc agtgaataga tt	32
<210> SEQ ID NO 336	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 336	
ttttatTTTA ctttttgta gtggg	25
<210> SEQ ID NO 337	
<211> LENGTH: 33	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 337	
gaaaatttcat cagtaaggttc agtgaataga ttt	33
<210> SEQ ID NO 338	
<211> LENGTH: 24	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 338	
tttatTTTAC ctTTTTGTTAG TGGG	24
<210> SEQ ID NO 339	
<211> LENGTH: 32	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 339	
ggaaatttca tcagtaaggtt cagtgaatag at	32

-continued

<210> SEQ ID NO 340	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 340	
tttttatttt accttttgtt agtgg	25
<210> SEQ ID NO 341	
<211> LENGTH: 32	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 341	
tggaaatttc atcagtaagt tcagtgaata ga	32
<210> SEQ ID NO 342	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 342	
ttttttatcc taccttttg tagtg	25
<210> SEQ ID NO 343	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 343	
aatttcatca gtaagttcag tgaat	25
<210> SEQ ID NO 344	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 344	
agattttta ttacccctt ttgtt	25
<210> SEQ ID NO 345	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 345	
aaatttcatc agtaagttca gtgaa	25
<210> SEQ ID NO 346	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 346	
tagatttttt attttacctt ttgtt	25
<210> SEQ ID NO 347	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	
<400> SEQUENCE: 347	

145

-continued

gaaatttcat cagtaagg ttc agtga

25

<210> SEQ ID NO 348
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 348

atagattttt tattttacct ttttg

25

<210> SEQ ID NO 349
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 349

ggaaatttca tcagtaagtt cagtgaatag att

33

<210> SEQ ID NO 350
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 350

ttttatTTTA ccttttGta gtgg

24

<210> SEQ ID NO 351
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 351

tggaaatttc atcagtaagt tcagtgaata gat

33

<210> SEQ ID NO 352
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 352

ttttatTTTA accttttGt agtg

24

<210> SEQ ID NO 353
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 353

aatttcatca gtaagg ttc agtgaata

26

<210> SEQ ID NO 354
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 354

gatttttat tttaccc ttgtta

24

<210> SEQ ID NO 355
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 355

US 9,273,294 B2

147

-continued

aaatccatc agtaagttca gtgaat	26
-----------------------------	----

<210> SEQ ID NO 356	
<211> LENGTH: 24	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	

<400> SEQUENCE: 356	
---------------------	--

agattttta ttttaccttt ttgt	24
---------------------------	----

<210> SEQ ID NO 357	
<211> LENGTH: 24	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	

<400> SEQUENCE: 357	
---------------------	--

agattttta ttttaccttt ttgt	24
---------------------------	----

<210> SEQ ID NO 358	
<211> LENGTH: 24	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	

<400> SEQUENCE: 358	
---------------------	--

agattttta ttttaccttt ttgt	24
---------------------------	----

<210> SEQ ID NO 359	
<211> LENGTH: 18	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	

<400> SEQUENCE: 359	
---------------------	--

tccaaaaat tatctaaa	18
--------------------	----

<210> SEQ ID NO 360	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	

<400> SEQUENCE: 360	
---------------------	--

tgcatacgaa gcatttaggag aagta	25
------------------------------	----

<210> SEQ ID NO 361	
<211> LENGTH: 15	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	

<400> SEQUENCE: 361	
---------------------	--

tgtgggtgt gtggg	15
-----------------	----

<210> SEQ ID NO 362	
<211> LENGTH: 26	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	

<400> SEQUENCE: 362	
---------------------	--

tgtgggtgt gtgtgtgggt gtgggt	26
-----------------------------	----

<210> SEQ ID NO 363	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: <i>Saccharomyces cerevisiae</i>	

148

<400> SEQUENCE: 363

gtctggccta tggtgctagt agtac

25

<210> SEQ ID NO 364

<211> LENGTH: 25

<212> TYPE: DNA

<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 364

acattattat tggtaaga ggact

25

<210> SEQ ID NO 365

<211> LENGTH: 25

<212> TYPE: DNA

<213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 365

gatacacacctt ccgtttctga cccat

25

<210> SEQ ID NO 366

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: *Homo sapiens*

<400> SEQUENCE: 366

gtgttgatga tgagaacctt atattatcct gaagagagg gatgacttaa aaatcatgct

60

caataggatt acgctgaggc cc

82

<210> SEQ ID NO 367

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: *Homo sapiens*

<400> SEQUENCE: 367

gggtcgatga tgagaagctt ctgtttctt gaagagagg gatgacttaa aaatcatgct

60

caataggatt atgctgaggc cc

82

<210> SEQ ID NO 368

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: *Homo sapiens*

<400> SEQUENCE: 368

gggtcaatga tgagaacctt atattgtcct gaagagagg gatgacttaa aaatcatgct

60

tagtaggatt acgctgaggc ct

82

<210> SEQ ID NO 369

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: *Homo sapiens*

<400> SEQUENCE: 369

gggtcgatga tgagaactt atattgtct gaagagagg gatgacttaa aaatcatgct

60

caataggatt acgctgaggc cc

82

<210> SEQ ID NO 370

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: *Homo sapiens*

<400> SEQUENCE: 370

-continued

ggatcgatga tgagaacctt atattgtcct gaagagaggat gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 371
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 371

gggtcaatga tgagaacctt atattgttct gaagagaggat gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 372
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 372

gggtcaatga gaaccttata ttgtcctgaa gagaggtgat aactaaaaa tcatgctcaa	60
taataggatt acgctgaggc cc	82

<210> SEQ ID NO 373
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 373

gggtcaatga tgagaacctt acattgttct gaagagaggat gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 374
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 374

gggtcgatga tgagaacctt atattgtcct gaagagaggat gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 375
<211> LENGTH: 81
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 375

gggtcgatga tgagaacctt atattgtctg aagagaggat atgacttaa aatcatgctc	60
aataggatta cgctgaggcc c	81

<210> SEQ ID NO 376
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 376

gggtcaatga tgagaacctt atattgtcct gaagagaggat gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 377

-continued

```

<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 377
gggtcgatga tgagaacctt atattgtcct gaagagaggt gatgacttaa aaatcatgct      60
caataggatt acgctgaggc cc                                         82

<210> SEQ ID NO 378
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 378
gggtcgatga tgagaacctt atattatcct gaagagaggt gatgacttaa aaatcatgct      60
caataggatt acgctgaggc cc                                         82

<210> SEQ ID NO 379
<211> LENGTH: 81
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 379
gggtcgatga tgagaaacctt atattgtctg aagagaggtg atgacttaaa aatcatgctc      60
aataggatta cgctgaggcc c                                         81

<210> SEQ ID NO 380
<211> LENGTH: 81
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 380
gggtcgatga tgagaacctt atatgttctg aagagaggtg atgacttaaa aatcatgctc      60
aataggatta cgctgaggcc c                                         81

<210> SEQ ID NO 381
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 381
gggtcaatga tgagaacctt atattatcct gaagagaggt gatgacttaa aaatcatgct      60
caataggatt acgctgaggc cc                                         82

<210> SEQ ID NO 382
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 382
gggtcgatga tgagaacctt atattgtcct gaagagaggt gatgacttaa aaatcatct      60
caaaaggatt atgctgaggc cc                                         82

<210> SEQ ID NO 383
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 383
gggtcgatga tgagaacctt atattgtcct gaagagaggt gatgacttaa aaatcatct      60

```

caaaaggatt atgctgaggc cc	82
--------------------------	----

<210> SEQ ID NO 384
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 384

gggtcgtatga tgagaacctt atattgtcct gaagagaggt gatgacttaa aaatcatttct	60
caaaaggatt atgctgaggc cc	82

<210> SEQ ID NO 385
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 385

gggtcgtatga tgagaacctt atattgtcct gaagagaggt gatgacttaa aaatcatgtct	60
caataggatt atgctgaggc cc	82

<210> SEQ ID NO 386
<211> LENGTH: 81
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 386

gggtcgtatga tgagaacctt atattttctg aagagaggtt atgacttaaa aatcatgtc	60
aataggatta cgctgaggcc c	81

<210> SEQ ID NO 387
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 387

gggtcaatga tgagaacctt atattgtcct gaagagaggt gatgacttaa aaatcatgtct	60
caataggatt acgctgagtc cc	82

<210> SEQ ID NO 388
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 388

gggtcaatga tgagaaccctt atattgtgtt gaagagaggtt gatgacttaa aattaccatg	60
ctcaatgatt acgctgaggcc cc	82

<210> SEQ ID NO 389
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 389

aggcgattatga tgagaacctt atattgtcct gaagagaggtt gatgacttaa aaatcatgcc	60
caataggatt acgctgaggcc cc	82

<210> SEQ ID NO 390
<211> LENGTH: 82
<212> TYPE: DNA

US 9,273,294 B2

157

-continued

158

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 390

gggtcagtga tgagaacctt atattgtcct gaagagaggt gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 391

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 391

gggtcaatga tgagaacctt atattgtcct gaagagaggt gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 392

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 392

gggtcaatga tgagaacctt atattgttct gaagagaggt gattatcaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 393

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 393

gggtcagtga tgagaacctt atattgtcct gaagaaaggt gatgacttaa aaatcatgct	60
caataggatt acactgaggc cc	82

<210> SEQ ID NO 394

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 394

gggtcaatga tgagaacctg atattgcct gaagagagat gatgacttaa aaatcatgtt	60
caataggatt acgctgaggc ct	82

<210> SEQ ID NO 395

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 395

gggtcaatga tgagaaccgt atattgtcct gaagagcggt gatgacttaa aaataatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 396

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 396

gggtcaatga tgagaacctt ataatgttct gaagagaggt gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 397
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 397

gggtcaatga tgagaacctt gtattatctt gaagagaggt gatgacttaa aaatcatgct	60
caataggatt acactgaggc cc	82

<210> SEQ ID NO 398
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 398

gggtcaatga tgagaacctt atattgtcct gaagagaggt gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 399
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 399

gggtgtatga tgagaacctt atattgtcct gaaaaaaagggt gatgacttaa acatcatgct	60
taatagtatt atgctgaagc cc	82

<210> SEQ ID NO 400
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 400

gggtcaatga tgagaacctt acattgtcct gaagagagat gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 401
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 401

gggtcaatga tgagaatctt atattgtcct gaagagaggt gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 402
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 402

gggtcgatga tgagaacctt atatttcct gaagagaggt gatgacttaa aaatcatgct	60
caataggatt acgctgaggc cc	82

<210> SEQ ID NO 403
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 403
 gggtcagtga tgagaacctt ctattgtcct gaagagaggat gatgacttaa aaatcatgct 60
 caataggatt acgctgaggc cc 82

<210> SEQ ID NO 404
 <211> LENGTH: 82
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 404
 gggtcgtatga tgagaacctt atattgttct gaagagaggat gatgacttaa aaatcatgct 60
 caataggatt acgctgaggc cc 82

<210> SEQ ID NO 405
 <211> LENGTH: 82
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 405
 gggtaatga tgagaacctt atattgtcct gaagagaggat gatgacttaa aaatcatgct 60
 caataggatt acgctgaggc cc 82

<210> SEQ ID NO 406
 <211> LENGTH: 82
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 406
 gggtaatga tgagaacctt atattgtcct gaagagcggt gatgacttaa aaatcatgct 60
 caataggatt acgctgaggc cc 82

<210> SEQ ID NO 407
 <211> LENGTH: 76
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 407
 gggtcaatga tgagatgtta ctttgaaagaaatgtatgc gtaaaaaatata agttcagttg 60
 gattacgctg aggccc 76

<210> SEQ ID NO 408
 <211> LENGTH: 83
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 408
 ggccgggtat gagaacttct cccactcaca ttcgagtttc ccgaccatga gatgactcca 60
 catgcactac catctgaggc cac 83

<210> SEQ ID NO 409
 <211> LENGTH: 74
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 409
 gtgtatgtat gacaactcggt aatgctgcat actccccaggat gggcggtgggg gaageccaacc 60
 ttggagagct gagc 74

163

164

-continued

<210> SEQ ID NO 410
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 410

cgcgtgatga cattctccgg aatcgctgta cggccttgat gaaagcacat ttgaaccctt 60
ttccatctga tt 72

<210> SEQ ID NO 411
<211> LENGTH: 564
<212> TYPE: DNA
<213> ORGANISM: Tupaia glis belangeri

<400> SEQUENCE: 411

gcagtttact ctcgcgagac gcgtggcggg aggcccttcgt ccaatccgcg cgcgcagcgc 60
ctttccccttt ataaggacac cgggcaggcg gcggggaggg agtggagggt gggccggga 120
cgggcggegga cccggtaatc taaccctgac tcacaagagg cgttagggcc gtgttttgc 180
tcccccgcgcg ctgtttttct cgctgacttt cagcgttcgg aaaaggccctg tggctatcg 240
ccatccacca tcctttctgg aacaaacaga caaaaaaaaaa aatgtcagct gctggccgt 300
tgtctctcc cggggccctgc ggtggccgc ageccgcctt ctcatcccc gcttcccgc 360
tagaggccgc ggtcgcccg gggcttcgc ggaggtgcc attgccccc cgaagagtt 420
ggctctgtca gccgcgggtc ctggggggc ccagggcgag gtttaggcct cgtggccgc 480
gggacacagcaa cggagcggtt ccccgcgagc ctgtgcgcgtt ccctgagccg tgggacttgc 540
accggggact ttgtcgac aatc 564

<210> SEQ ID NO 412
<211> LENGTH: 545
<212> TYPE: DNA
<213> ORGANISM: Chinchilla brevicaudata

<400> SEQUENCE: 412

cgtgagacca agtgtcgca gagccgtggc aaggcttcag ccaatccgag cgggcgcctc 60
ctggccctctt tataaggagc ctgtcgccac acgtcccgcc gttgagaatg gtggccggg 120
aggggagggtg ggcatgttt gtctaaccctt aactaggagg aggacgttgg cgcgtgtttt 180
ttgttcccccg cgcgctgtt ttctcgctga ctttcagegtt gggaaaaagg cttggccctgc 240
cgtcgaccac tgtctaattt aaagcaaaaca aaaaatgtca gctgtggccgg tccggccctc 300
ccgggttacctt gccggcggcc gccgggttgg ccccccggcc cggcccgagg ccacgggtgg 360
cgccggggctt ctccggggagc gccatggccg cccggcggcc gttcgctctg tcagggccgg 420
gtcgcgccggg ggccgggggg gaggcttggc cccggatggcc gcaaggaaatgaaacggagcc 480
tgtccctgtt caccggggccg ttctcgatc tggtggaaatg gcccccggcc tcgggttccctt 540
caaggc 545

<210> SEQ ID NO 413
<211> LENGTH: 546
<212> TYPE: DNA
<213> ORGANISM: Geomys breviceps

<400> SEQUENCE: 413

agaggaacca actctcgca gagccgtggc tggagctcag ctaatacgca ggcgcggcac 60
ggccggcccttta taaggcgccgg ggcgcggccggtt ccggccggcc gttggccgggaa gggggggctg 120

gtccccactct	tctaacccta	agggtgtcgg	ctgttaggcgc	cgtgctttt	acttcccccgc	180
gegctgtttt	tctggctggc	tttcagcgag	cggaaaaaagc	tttggtctac	aggccactca	240
ctttgtatcc	cgaaaccaa	ttgaaaaaaaaa	aaaatgccag	ctccggccgg	tccacccctc	300
ccggggctct	cgccccggc	cgccccggc	aaccccccgc	gaccggcctg	aggccacggc	360
cgggccgggg	cctctgcggg	ggtgccatt	gcccggcgg	agagtttaggc	tctgtcagcc	420
gccccatccg	cgccccgggg	gccccggcgg	gacgcccata	cgccaggaca	gcaacggAAC	480
cgcccccttc	gccccgtgcg	cttccggag	ctgtggatg	agcacccggg	gtcggtcct	540
acagtt						546

<210> SEQ ID NO 414
<211> LENGTH: 496
<212> TYPE: DNA
<213> ORGANISM: Microtus ochrogaster

<400> SEQUENCE: 414						
gagcgcgaga	gtgcaaacac	gggcgagagt	tgggcgcgg	ccaatcagcg	agcgcgcgtga	60
cccgaggatt	taagggcg	ccgacgggg	gacggggcgc	gcgcgcctct	tctaacccta	120
aaaaactggag	ctgttaggtgt	tgctctttca	gcgtcgcccg	ctgtttttct	cgctggctt	180
cagcgggcca	gaaagttcag	acctctcagc	agatcgtcgc	gtcgttctca	accacaaaaa	240
atgccagcgc	aaagcgcgtc	agcctagaac	cttgcggccc	cgggcccgc	agcccccgcac	300
ccgcctttag	gccgcgggtt	gcctggagtt	ctccggactc	cgctggccc	gcaagagtt	360
cgtctctgtc	agccgcggag	tatcaggggc	tggggccagg	cccggacagc	gtcgcaagta	420
cagtaacgga	gctggtcctt	gttcgggtggc	ttccctgagc	tgttaggaagt	acacccagag	480
ctcggctcct	acaacc					496

<210> SEQ ID NO 415
<211> LENGTH: 397
<212> TYPE: DNA
<213> ORGANISM: Mus spretus

<400> SEQUENCE: 415						
acttaaccct	gatttcatt	agctgtgggt	tctggtcttt	tgttcttcgc	ccgctgtttt	60
ttcgcgtac	ttccagcgga	ccagtaaat	ccagacctgc	agcggggcac	cgcgcggtcc	120
cgagcctcaa	aaacaaacgt	cagcgcagga	gcttcaggtt	cgccgggagc	tccggggcgt	180
cggggccccc	agtcccgta	ccgcctacag	gcccggccgc	gcctggggtc	ttaggactcc	240
gtgcgcgcgc	cgaaagagctc	gcctctgtca	gcccgggggc	gcccggggct	ggggccaggc	300
cggggcggcgc	ccgcgcggac	aggaatggaa	ctggtcccc	tgtttggtgt	cttacctgag	360
ctgtggaaag	tgcacccgga	actcggttct	cacaacc			397

<210> SEQ ID NO 416
<211> LENGTH: 397
<212> TYPE: DNA
<213> ORGANISM: Mus musculus castaneus

<400> SEQUENCE: 416						
acttaaccct	gatttcatt	agctgtgggt	tctggtcttt	tgttctccgc	ccgctgtttt	60
ttcgcgtac	ttccagcggg	ccagaaaaat	ccagacctgc	agcggggcac	cgcgcggtcc	120
cgagcctcaa	aaacaaacgt	cagcgcagga	gctccaggtt	cgccgggagc	tccggggcgc	180
cggggccccc	agtcccgta	ccgcctacag	gcccggccgc	gcctggggtc	ttaggactcc	240

gctgcccggc cgaagagctc gcctctgtca gccgcggggc gccggggct gggggcaggc 300
 cgggcgagcg ccgcgaggac aggaatggaa ctggtccccg tggcggtgt cttacctgag 360
 ctgtggaaag tgccacccgga actcggttct cacaacc 397

<210> SEQ ID NO 417
 <211> LENGTH: 541
 <212> TYPE: DNA
 <213> ORGANISM: Mustela putorius furo

<400> SEQUENCE: 417

ccggctccgg	ctctcgcgag	agccgagaca	ggggctccgg	ccaatcgccg	cgggcggcgg	60
ccgcgtccctt	tatagggaga	cgcggccggg	tgcagttcgg	gttgcggagg	gtgggctcg	120
gaggggtggc	ggtcattttc	tgtctaaacc	taactgaaac	ggcgttaggc	gtcgttgttt	180
tgttccccgc	acgctgtttt	tctcgctgac	tttcagcggg	cggaaaagcc	ttggcctact	240
gcacacacacc	atccagtttg	gagcaaacaa	aaaatgtcag	cggctggcct	gtcgccccct	300
cccgggagcc	tgccggcgact	cgcggcgtta	gcccccgcat	ccgcctgg	ggccgcggc	360
ggcccgggggc	ttctccggag	gcaccatttgc	ccgtcgcgaa	gagttggct	ctgtcagccg	420
cgggacccctt	ggggggccaag	ggcgaggctc	tggccgcagg	gagagaaacg	gagcgggtcc	480
cctcgegcgg	tgcggttccc	tgagctgtgg	gacttgcacc	cgggactagg	ctcacacaca	540
c						541

<210> SEQ ID NO 418
 <211> LENGTH: 542
 <212> TYPE: DNA
 <213> ORGANISM: Procyon lotor

<400> SEQUENCE: 418

ctgaggccgg	ctctcgcgag	agccgagaca	ggggctccgg	ccaatcgccg	cgggcggcgg	60
ccgcgtccctt	tatagggaga	cgcggccggc	tgtagttcgg	gttgcggagg	gtgggctcg	120
gaggggtggc	ggtcgtttt	tgtctaaacc	taactgagaa	ggcgttaggc	gtcgttgttt	180
tgttccccgc	acgctgtttt	tctcgctgac	tttcagcggg	cggaaaagcc	tcggcctact	240
gcacacacacc	atccagtttg	gagcaaacaa	aaaatgtcag	cgcggcgcct	gtcgccccct	300
cccgggatcc	tgccgtggct	cgcggcgtta	gcccccgcat	ccgcctgg	ggccgcggc	360
ggcccgggggc	ttctccggag	gcaccatttgc	ccgtcgcgaa	gagttggct	ctgtcagccg	420
cgggacccttt	ggggggccaag	ggcgaggctc	tggccgcagg	gagagaaac	ggagcgggtc	480
cccttgcgcg	gtcggttccc	ctgagctgtg	gacttgcac	cgggacttag	gtcacacac	540
at						542

<210> SEQ ID NO 419
 <211> LENGTH: 548
 <212> TYPE: DNA
 <213> ORGANISM: Suncus murinus

<400> SEQUENCE: 419

gactttaaac	atcgcgagat	ttgcagcggg	accatctcag	ccaatcagcg	cggccggcgg	60
caactgtact	taagcgaga	cgcggcgccg	ccatgttggc	gggttgcggg	agctgcgagc	120
ggccgtctcg	tctaacccta	aagagaaagg	cgttaggtgt	tggccttggc	gactcgcccg	180
ctgttttttg	gctgggtttc	agcgggtgaa	gaggcccaag	acctaccggc	acccaccgtc	240

-continued

tagtgtctta	agggcacaaa	gtcctgccc	ccacccttcg	aggagcgaaa	cccaaaaaag	300
tca	ccccctgc	ccgcgtctc	gcctctcg	aacccgcctc	cgtcccagcc	360
ccccaggccg	cggtcggtcc	gggtttcttc	ggaagtcccg	ttgcgtcgc	gaagagttcg	420
cctctgtcg	ccgcggggct	tggggccagg	gacgggacc	tgtccgcagg	gagagaaact	480
ggagccgggc	cctccacgg	gcctccccga	gctgtggat	ctgcacccgg	gactcgaacc	540
ctacactt						548

<210> SEQ ID NO 420

<211> LENGTH: 545

<212> TYPE: DNA

<213> ORGANISM: Dasypus novemcinctus

<400> SEQUENCE: 420

ggctctcg	agagccagt	gccccgtggc	gggccteggc	aatccgcgc	cgcgcctcg	60
ttcccttat	aaggaggct	cgcgcgcca	gccccgggtt	gccccgggag	ggcccgagg	120
gggtgagcgt	ccattatcg	ctaaccctaa	ctgagatggg	cgtaggcc	gcgccttgc	180
ttcccgccg	ctgttttct	cgctgacttt	cagccccgg	aaaagctcg	gcctactgcc	240
gtctactgtc	gtatctggag	caaaca	atgtcagcc	ctggtecg	cgc	300
ggaaacctgc	ggtggctcg	ccgcctg	ccccgc	gcctagaggc	cgcggcc	360
ccggggcttc	tccggaggca	cccaatgcag	ccgcga	ttaggctctg	tcagccgcgg	420
atcccgccgg	ggccaagggt	gaggcttagg	ccgcggcc	caggaagaaa	aaccgagcga	480
gttctcacgc	gcgggtcg	tccctgagct	gtgggtcg	ccctgggac	tcggctcaga	540
cacgt						545

<210> SEQ ID NO 421

<211> LENGTH: 614

<212> TYPE: DNA

<213> ORGANISM: Dasyurus hallucatus

<400> SEQUENCE: 421

cgtttggatc	ctttggctcg	tcttctggcg	gctgcggcga	ccaatgagcg	cgtccggggc	60
cgggttttg	ggaaggata	agagagggt	gcaggcg	cggtgtgc	ggacgggctg	120
cgtgggggg	tccgtccgtc	ctggcacatc	taaccctaa	tgcgcgtgg	ttgaagtggc	180
ttctcctggg	cgatcgctcg	ctgttttgt	ggctggctt	cagccccgt	gaggagccgg	240
gagcggaggc	ggaggaccga	cccaaaaacg	tca	ccgcggaggc	ccgcgtcg	300
cccgccgc	ctgtccggc	caggccccgg	cccgaa	ctggagacaa	ctccgcagg	360
gtctgegtcg	ccgcggggag	ccccggctgc	ccacgt	ccgcggccg	tctcgcc	420
cctgcgtcg	gggcgcccac	tgcggccgc	aagagctcg	ctctgtcagc	ctcggtgc	480
cgtggggccg	cggtcgagcc	ctaaggccgg	cggtggggct	gggggtcg	ggagagtaac	540
cgtgagccgg	cccccagcc	tcagggcg	ccctcgagct	atgggagctg	ccccggca	600
cggctcg	accc					614

<210> SEQ ID NO 422

<211> LENGTH: 554

<212> TYPE: DNA

<213> ORGANISM: Trichechus manatus

<400> SEQUENCE: 422

agatctgctg	tcgcgag	cagtggcg	aaagcctgg	ccatcccg	ccggccggcg	60
------------	---------	----------	-----------	----------	------------	----

-continued

cctctccctt tataaggaga cttggcgccc gaggcttggc gtggaggggtt gaggatggcg	120
ccccccgggtc gggcagtgggt ctttttgtt ctaaccctaa ctggcaaggg cgttaggtgct	180
gtgttttgtt tccccgcgcg ttgtttttct cgctgacttt cagcggggcgg gaaaagccct	240
ggccttaccgc cgtctaccga tagtttggag caaacaaaaa aatgtcagcc gctggccgt	300
cacccctccc gggAACCTGT ggtggctcgc ccgcccagcc ccgcgecccg cctggaggcc	360
gccccgtggcc tggggcttct ccggagggttc ccattgcgcg cgcgaaaggt taggctctgt	420
cagccgcggg tcctgcggga accaaggggcg aggcttaggc ctccctgaacg cagggagaga	480
aatggagcga ttccccgagt acgtgtgttt ccctgagttt tggatgtgc gtccgggact	540
cagctccgac aggt	554

<210> SEQ ID NO 423

<211> LENGTH: 538

<212> TYPE: DNA

<213> ORGANISM: Anodorhynchus hyacinthinus

<400> SEQUENCE: 423

cagccgcagc caatgcggca gaggtgggagc ccgcattctga ccaatggagg cgccgtgggc	60
gtggccgcgg agggtttaag aggaggcccg agggggccgc ttgtcgctg gcggatgggg	120
aggctccagt ctcactaacc ctaatggctg ccgcgcgtgc cccgcaccc gtccgcgttt	180
ttattegctg actttcagcg gacggggggga gcccgcctggg ggggaagggg tttcaatca	240
aaaaaaegtca gcgaagggtc tccccagccc agccgcacctt ggggtctccg tccccccacg	300
cagccggggg octgecgccg aggetccctc cgccgcactt cacggaggcc gcggtcggcc	360
ggtgtccgccc actgeccgcg cgaagagttc gtctctgtca gcctcgccgg cggtggggag	420
cgagagggct cgtccccgcg ccggggaccc cagcagagca aaacggagcg gcgtctcg	480
cacagccgcc gcgcttccct caaccgtggg atgcgcggac ggccgcgtt cgacaccc	538

<210> SEQ ID NO 424

<211> LENGTH: 513

<212> TYPE: DNA

<213> ORGANISM: Chelydra serpentina

<400> SEQUENCE: 424

cccgccgagc caatggaat agaggagact cccgctagcc aatccatgcg cgggaggcg	60
ggacgggtga aggttatataa gacccgcggc caggcgggtc tgaccgctgc ggccgcaggt	120
gggggctcag tctttctaacc cctaagcgaa atgtgacccc tccccgctgc agccgtccgc	180
tgttttactc gctgactttc agcggacggg gggagcgggtt ggagacgcaca accaaaaaac	240
gtcagcgagg ggcctccccc tcccacgcgg acctgggcct gtgggtgggc ccgcgcagcga	300
agtccccgcg gccccggccc ggtgaggccg cggtcagccg gtcgcgcaca ctgcgcgc	360
gaagagttcg tctctgtcaag cctcgggggc ggccgggggtt gaaggggggg tccccgaccc	420
gtcggccggg agagcaaacg tgagcggcag cccctgcgc accgcctcc cctaagctgt	480
ggggcccgcg gtcggggctg cgctcagaca cgc	513

<210> SEQ ID NO 425

<211> LENGTH: 520

<212> TYPE: DNA

<213> ORGANISM: Bufo japonicus

<400> SEQUENCE: 425

-continued

gaacgcacg ctacgggtag cagtaagggt agaccgataa ccaatcaaat ggtaatacat	60
acattacgta attttatgtt taaatacgtt tgttttttt ccggtagtt aatttagaggg	120
atggaaaggt tccgctttagt ctaaccctaa tattgggggt ctgtgaaaa cctcttaag	180
atatgegtgt tgtttattt gctgacttc agcgccatt gagaggagtt gctgccagg	240
actaaaaaat gtcagctggg agtccttctt ctcccttattt tctgcctcac aacctggact	300
cttttattttag cggtccccca tttgtcgagg cegcagtcg tcttgttctt atacgctgct	360
gttgcgaaga gttcgctctt gtcagccctt gggcaacgc cttgaatttg gagagcctgg	420
aatgttaaca aggggtaggg aaaataacga gagctgagtt ggcttctctt gtgctgtcc	480
ttagctgtgg aacttgcattt cgcagtcggc tctgacactt	520

<210> SEQ ID NO 426

<211> LENGTH: 507

<212> TYPE: DNA

<213> ORGANISM: Ceratophrys ornata

<400> SEQUENCE: 426

gtaatagggtt gtaaggttcc cgccacgctc cgtctggaca ggcgcagccgg cgagcggtga	60
cgtcatgtta cgtataaaaag tcagacccgg ccaatgcggc ttacagtggg aataggaggg	120
agtctatattt tctaaccctta atataccgg ttcagggctc ttatgtggcg ctcgttctt	180
tgccgggttgc ctttcagcgg ggcggaaagac tcagagaacg gaggacaaa aaacggcagc	240
cgccggccctt cctgttccca ccattccacg tttccacac tgcgcctggg ttctcaactca	300
agtgttcggc agcttccact tacgaggccg cggcttacccg ctgtcaactgg tagtcgcgaa	360
gagttcgtct ctgtcagccct tgggagccgc ggacggagta tgaggccag taatgagac	420
aggaaagagt aaagcgagcc ggcgtacttg tcctatctgc cgctcctaag ctgtggcg	480
tgttagggtagt acaaggctcc gacattt	507

<210> SEQ ID NO 427

<211> LENGTH: 499

<212> TYPE: DNA

<213> ORGANISM: Pyxicephalus adspersus

<400> SEQUENCE: 427

ctgatccacc ctaacccttc cctcctgagg tcaggccgtc caataaacgg agagcagtga	60
cgtcacatgt agtataaaaag aacatgtcg cagaggccgc ctccagcggt aataggagag	120
ttctatccctt ctaaccctta tgcacagacc cctcgctgtc ttcatgtc gtttttttc	180
tcgctgactt tcageggcg aaagagcaat ggaagctcaag gactaaaaaa cgtcagccgt	240
aggcttccctt atagecccgag ccctgcctgt cagtgtgcgc ggccctctgtc cgcaatgtcc	300
gcagcgcctt octatgaggc cgcagtctgc caataccccc ggcagccgc aagagcttgt	360
ctctgtcagc ctttggcgct gggggggagg gggggaggcc gctgtggca gctgagaata	420
aagcgagccc agctgccccg ctctgttcca ctgccttgc gctgtgggt tggtgaattt	480
cagcatggctt ccgacaactt	499

<210> SEQ ID NO 428

<211> LENGTH: 565

<212> TYPE: DNA

<213> ORGANISM: Dermophis mexicanus

<400> SEQUENCE: 428

tcctacagcc gcagacgcaa ttgaaaaaac gtgcgaacca atcagctgcc ggtaggt	60
--	----

gcgtcactgg tgtgcgggtg aaaatgaatg tataaataca ggagcacgta accatatcac 120
 ttctccggaa gaggggcggt ttctctgtct tctaacccta atgcgggtct tcggcagaag 180
 ctctccactg cgtacgctca ctgttttct agctaacttt cagttagcag ggagagcgaa 240
 gtccagtttc acgacaacgg agaaaaaatg tttagctgggg aacgtccctt tcccagagac 300
 ccggcgccgtc cttttcttc ctggggcccg ttggcatage ccctggctc ctcgtctat 360
 aggcccggtt cagctcggtt cccagctcg gcaggggttc cactgtgcc gcgaagagtt 420
 cgccctgttc agcattgagg ttggccggat agaataggcg ggctcgccg agcgccggg 480
 aaagagcaaa tggtaactg ggtgcctgtt ggggtcgcgt ccctgaagag tgggaagtgc 540
 gatctgtgtt octgttcaga cacac 565

<210> SEQ ID NO 429

<211> LENGTH: 556

<212> TYPE: DNA

<213> ORGANISM: Herpele squalostoma

<400> SEQUENCE: 429

tgctaacgcc ggctgcagac gcaacttaaa ttctgcgaac caatcagctt ccagctagag 60
 ggccgcgttag ttggaatggg tttataaaaa gggaaaccag ccacagaacc attctcttg 120
 gagccccccg atttctcttc cttctaaacc taatgcgggtt cttaggcac agttctccgg 180
 gtgcgtcgc ttgtttctg gctaactttc agcgagcggg gagagcgaag ccgtggttta 240
 cgacgataga ggagaaaaaaa ttgttagctgg ggaacgtccc tttcccgaga gcccgcgcca 300
 tcctcttcct cgggcccatt ggcgatagcc cccggctcc ctcgctcacc aggccgcgg 360
 cagccccccg cttggctctg cttaggcgc caatgcgtcc gcaagagtt cgtctctgat 420
 tgccttgagg tagccggct cgaatagggtt ggctcgccg gatgcgcagg aaagagcaaa 480
 acagtgaact gggcggtgtc tgggtcgcgt tccctgaagt gtggatgtg cgtatgtcc 540
 gcttggtagt acattt 556

<210> SEQ ID NO 430

<211> LENGTH: 554

<212> TYPE: DNA

<213> ORGANISM: Typhlonectes natans

<400> SEQUENCE: 430

accttaggat ttgcaccaa tcagctgccg actggaggaa ccaatcagct gccggcttga 60
 ggccgcgcgtt gaaaacgaga gtataaaaatg cagaacttgc actcatagca ttgtcatcc 120
 ggagaggggc gttttcttct ttctctaaacc ctaatgtatt gttggcag cagctcttc 180
 ggtatgctcg ctgttttgtt ggctaaactt cagcgagcag agggcgaagt cgaatttccg 240
 acaagggaga aaaaatgtta gcccggaaac gccccttcc cgaatgccc tgccgtcctt 300
 cctctctctt gggcccggtt gcgatagccc cccggctccc tcgctcttta gcccgcggc 360
 agtccgggcc cttgctctgg catgagggtcc attgctgccg cgaagagttc gtctctgtca 420
 gcttggatgtt ggccagcatg gaattggcg gcttggcg ggcgcgggaa aaaagcaaat 480
 ggtgaacttag gtgcgtgtt tggtcgtt cctgaagcgt ggaatgtgcc atctgtgcgc 540
 tagttcatac acac 554

<210> SEQ ID NO 431

<211> LENGTH: 312

<212> TYPE: DNA

-continued

<213> ORGANISM: Oryzias latipes

<400> SEQUENCE: 431

gcgggggtgtt	ctacctaacc	ctaatttagag	gctgcctcg	gtacttaacg	tatgtgttt	60
tgttgtttct	ggcttcagc	agactacatg	aggcggtggg	cgtgaagctt	aaaaatatcc	120
gtacaaaaaa	agccagaaaa	gactccccgt	cgcgctcagt	tccctgtcg	aaacgcgcg	180
gtcagctcg	ctgctcgaa	gagttcgct	ctgttgttc	ggggattgtc	aacagctgag	240
cagataaaaa	tgagcaaggc	gatectgcgg	aacctcatgt	ggtccggtgc	ggtatcc tac	300
gctcagacaa	at					312

<210> SEQ ID NO 432

<211> LENGTH: 348

<212> TYPE: DNA

<213> ORGANISM: Gasterosteus aculeatus

<400> SEQUENCE: 432

acggagtg	tcttctaacc	ctaaataacgg	aggcccctc	gtactcaacg	tttgcgttt	60
ttttctgg	ttcagtaaa	ctacgggagg	ggctgacgcg	acgctggaa	cgttccgaa	120
cgacaaccaa	aaaaaaagcca	agatgaccac	tccgtcg	tca	gtgtccc	180
ccgcgaattt	cctgcccgtgg	tcggcttgc	ctgcccgc	gagttcg	tct	240
ggtgttctca	tggcgggact	tgtgataact	gagcagagta	aaactgagca	gggcgactct	300
cccagatcg	tccagtgtac	cggtcagaaa	gccccgc	ctc	aaacaccc	348

<210> SEQ ID NO 433

<211> LENGTH: 325

<212> TYPE: DNA

<213> ORGANISM: Takifugu rubripes

<400> SEQUENCE: 433

acggagtg	tcttctaacc	ctaaattatc	tcggctcc	gtactcg	tttgcgttt	60
ttgtctgg	ttcaggaaac	tacagggagt	cttggacgtc	tccgttca	acg gatcaaaaaa	120
gccaagaaaa	tcactccgtc	gcgttcaggt	ccccccagg	aacaccgaga	gccctgttgt	180
ggtcagtccg	gctgccc	caa agagttgg	tctgtgtc	cggtgtctt	gccccatcac	240
caaggactga	acagagaaac	agtgagcgt	gtgacttac	cggttcttcc	aatgtcccgg	300
ttaggatacc	caagctaaa	cactc				325

What is claimed is:

1. A method for increasing telomere length comprising:
 providing a yeast cell expressing a telomerase ribonucleo-
 protein comprising a yeast telomerase RNA;
 providing a nucleic acid encoding, a C/D box snoRNA
 guide RNA that causes a 2'-O-methylation modification
 of nucleotide A804 or A805 in the yeast telomerase RNA
 to the cell in a manner that causes the guide RNA to be
 expressed in the cell.

50 2. The method of claim 1, wherein the yeast telomerase RNA is encoded by a nucleic acid comprising SEQ ID NO: 282.

3. The method of claim 1, where in the C/D box snoRNA is transcribed from a nucleic acid sequence comprising a sequence selected from SEQ ID NOS: 321 or 322.

55 4. The method of claim 1, wherein the process is performed in vivo.

* * * * *